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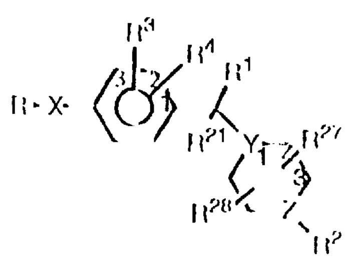

(I)

(57) Abstract

Di-N-substituted piperazine or 1,4 di-substituted piperidine compounds in accordance with formula I (including all isomers, salts, esters, and solvates) wherein R, R^1, R^2, R^3, R^4, R^{21}, R^{27}, R^{28}, X, Y and Z as defined herein are muscarinic antagonists useful for treating cognitive disorders such as Alzheimer's disease. Pharmaceutical compositions and methods of preparation are also disclosed. Also disclosed are synergistic combinations of compounds of the above formula with acetylcholinesterase inhibitors.

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MUSCARINIC ANTAGONISTS

BACKGROUND OF THE INVENTION

The present invention relates to di-N-substituted piperazines and 1,4-di-substituted piperidines useful in the treatment of cognitive disorders, pharmaceutical compositions containing the compounds, methods of treatment using the compounds, and to the use of said compounds in combination with acetylcholinesterase inhibitors.

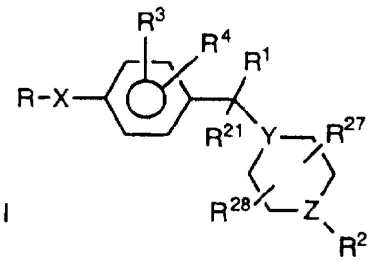
Alzheimer's disease and other cognitive disorders have received much attention lately, yet treatments for these diseases have not been very successful. According to Melchiorre et al. (J. Med. Chem. (1993), 36, 3734-3737), compounds that selectively antagonize M2 muscarinic receptors, especially in relation to M1 muscarinic receptors, should possess activity against cognitive disorders. Baumgold et al. (Eur. J. of Pharmacol., 251, (1994) 315-317) disclose 3-α-chloroimperialine as a highly selective m2 muscarinic antagonist.

The present invention is predicated on the discovery of a class of di-N-substituted piperazines and 1,4-di-substituted piperidines, some of which have m2 selectivity even higher than that of 3-α-chloroimperialine. Logemann et al (Brit. J. Pharmacol. (1961), 17, 286-296) describe certain di-N-substituted piperazines, but these are different from the

inventive compounds of the present invention. Furthermore, the compounds of Logemann et al. are not disclosed to have activity against cognitive disorders.

SUMMARY OF THE INVENTION

The present invention relates to compounds according to the structural formula I,

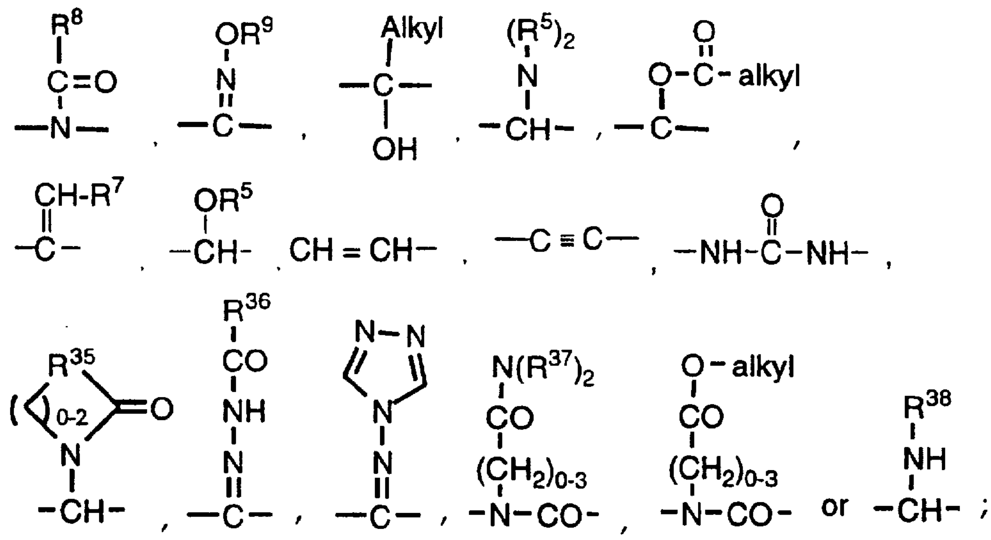


I

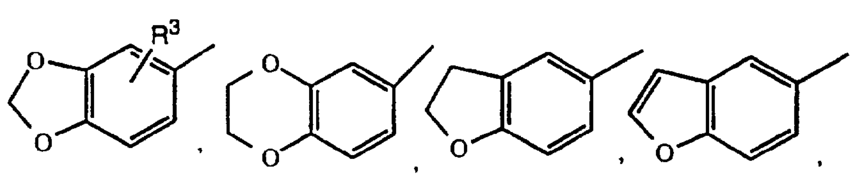
including all isomers and pharmaceutically acceptable salts, esters, and solvates thereof,

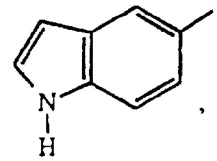
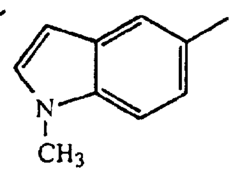
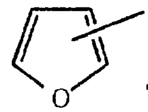
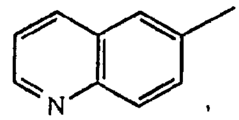
wherein one of Y and Z is N and the other is N, CH, or C-alkyl;

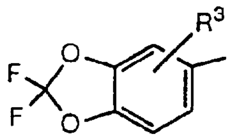
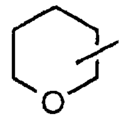
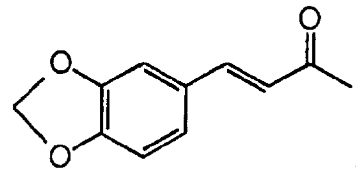
X is -O-, -S-, -SO-, $-SO_2-$, $-NR^6-$, -CO-, $-CH_2-$, -CS-, $-C(OR^5)_2-$, $-C(SR^5)_2-$, $-CONR^{20}-$, $-C(alkyl)_2-$, -C(H)(alkyl)-, $-NR^{20}-SO_2-$, $-SO_2-NR^{20}-$, $-NR^{20}CO-$, -O-CO-NH-, -NH-CO-O-,

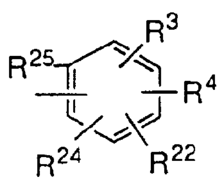
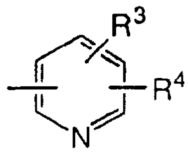
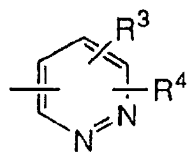
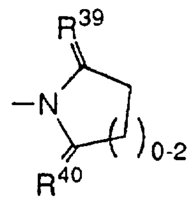


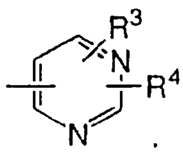
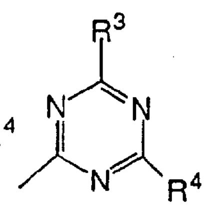
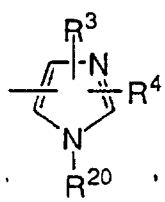
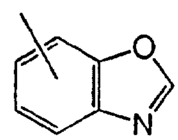
R is

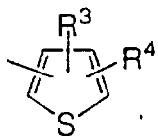
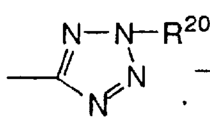
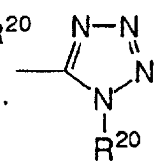
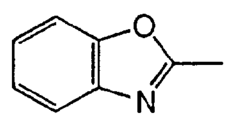


, , , ,

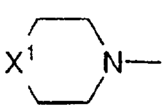
, , ,

, , , ,

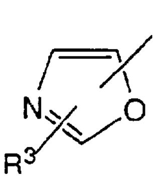
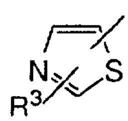
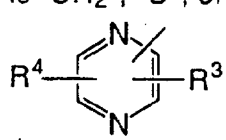
, , , ,

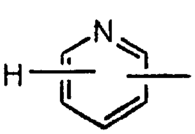
, , , ,

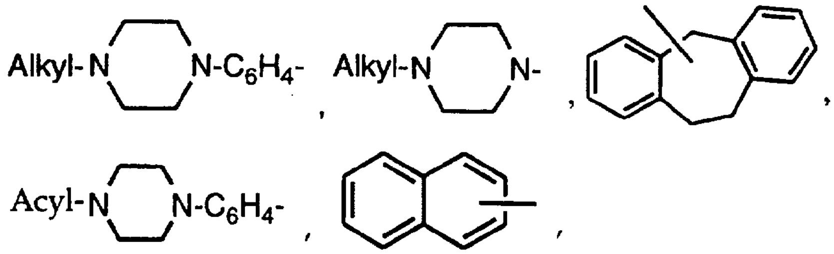
$R^7-C\equiv C-CH(R^8)-$, $R^7-CH_2-C\equiv C-$, $(R^8)_2C=C=C(R^7)-$,



(wherein X^1 is $-CH_2-$, $-O-$, or $-NR^7-$),

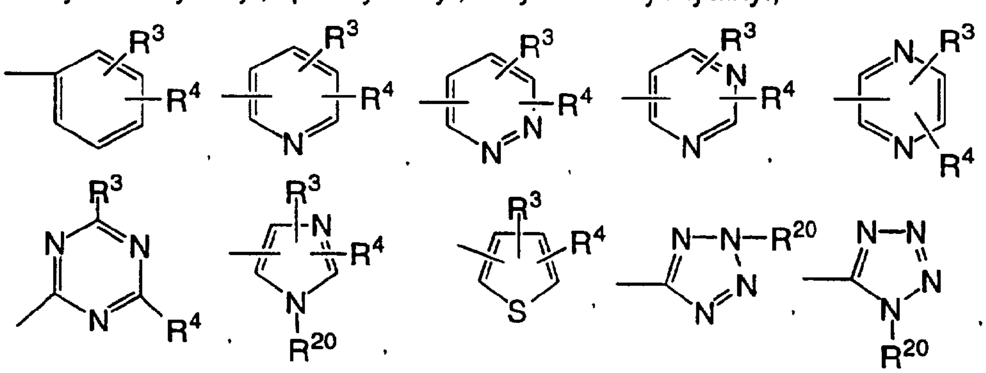
, , , Alkyl—$N(R^8)$—C(=O)—,

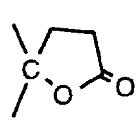
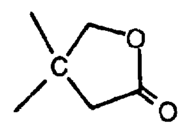
Alkyl-N(alkyl)-CONH— ,



hydrogen, acyl, alkyl, alkoxy, alkenyl, cycloalkyl, cycloalkyl substituted with one or two groups selected from the group consisting of alkyl and carbonyl, cycloalkenyl, bicycloalkyl, arylalkenyl, benzyl, benzyl substituted with up to three independently selected R^3 groups, cycloalkylalkyl, polyhaloacyl, benzyloxyalkyl, hydroxyC_2-C_{20}alkyl, alkenylcarbonyl, alkylarylsulfonyl, alkoxycarbonylaminoacyl, alkylsulfonyl, or arylsulfonyl, additionally, when X is $-CH_2-$, R may also be -OH; in further addition, when X is not N, R may also be hydroxymethyl, in further addition, R and X may combine to form the group Prot-$(NOAA)_r$-NH- wherein r is an integer of 1 to 4, Prot is a nitrogen protecting group and when r is 1, NOAA is a naturally occuring amino acid or an enantiomer thereof, or when r is 2 to 4, each NOAA is a peptide of an independently selected naturally occuring amino acid or an enantiomer thereof;

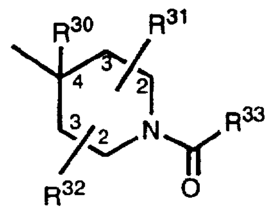
R^1 and R^{21} are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkyl, alkynyl, cyano, aminoalkyl, alkoxycarbonyl, aminocarbonyl, hydroxyamidino, alkoxycarbonylalkyl, phenyl alkyl, alkylcarbonlyoxyalkyl,



H, —OH, (provided R^1 and R^{21} are both not —OH and Y is not N), formyl, —CO alkyl, -COacyl, —COaryl, and hydroxyalkyl; additionally R^1 and R^{21} together may form the group $=CH_2$, $=N\text{-}OR^5$, =N-CN, $=N\text{-}N(R^5)_2$, =CH-alkyl, alkylene, $=\overset{\text{alkyl}}{\overset{|}{C}}-\text{alkyl}$ or $=C(\text{halo})_2$; in further addition, R^1 and R^{21} together with the carbon atom to which they are attached may form the group  or 

or R^1 and R^{21} together with the carbon atom to which they are attached may form a saturated heterocyclic ring containing 3 to 7 carbon atoms, one or more of which may be optionally substituted by alkyl, and one or two groups independently selected from S, O, and $N\text{-}R^{20}$;

R^2 is



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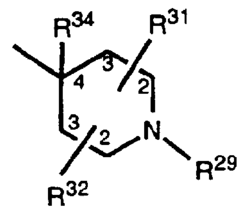


;

R^3, R^4, R^{22}, R^{24}, and R^{25} are independently selected from the group consisting of alkyl, H, halo, alkoxy, benzyloxy, benzyloxy substituted by nitro or aminoalkyl, haloalkyl, polyhaloalkyl, nitro, cyano, sulfonyl, hydroxy, amino, alkylamino, formyl, alkylthio, polyhaloalkoxy, acyloxy, trialkylsilyl, alkylsulfonyl, arylsulfonyl, acyl, alkoxycarbonyl alkylsulfinyl; $-OCONH_2$, -OCONH-alkyl, alkylaminoalkyl, dialkylaminoalkyl, -COOH, $-CON(R^{20})_2$, $-OCON(\text{alkyl})_2$, -NHCOO-alkyl, -NHCO-alkyl, phenyl, hydroxyalkyl, or morpholino;

each R^5 and R^6 is independently selected from the group consisting of H and alkyl, provided that when X is $C(OR^5)_2$ or $C(SR^5)_2$, both R^5 groups cannot be H, and in addition, when X is $C(OR^5)_2$ or $C(SR^5)_2$, the two R^5 groups in X may be joined to form $—(CR^{20}{}_2)_p$- wherein p is an integer of 2 to 4;

R^7 is independently selected from the group consisting of H, alkyl, arylalkyl, cycloalkyl, aryl and aryl substituted with R^3 and R^4 as defined herein;

each R^8 is independently selected from the group consisting of H, hydroxyalkyl or alkyl, or two R^8 groups may be joined to form an alkylene group;

R^9 is H, alkyl, aralkyl, or acyl;

R^{20} is H, aryl or alkyl;

R^{27} and R^{28} are independently selected from the group consisting of H, alkyl, hydroxyalkyl, arylalkyl, aminoalkyl, haloalkyl, thioalkyl, alkylthioalkyl, carboxyalkyl, imidazolyalkyl, and indolyalkyl; or R^{27} and R^{28} may combine to form an alkylene group;

R^{29} is H, alkyl, -CO-alkyl, -CO-cycloalkyl, alkoxycarbonyl, amino-carbonyl, aryloxycarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylsulfonyl, arysulfonyl or $-SO_2-NH-R^{20}$;

R^{30} is H, alkyl, aryl, cycloalkyl, hydroxyalkyl, aminoalkyl, $-COOR^{20}$, $-CON(R^{20})_2$ or cyano;

R^{31} and R^{32} are the same as R^{30} and in addition, two R^{30}, R^{31} and R^{32} groups may form the group $-(CH_2)_r-$ (wherein r is 1 to 6), in further addition, R^{31} and R^{32} can also be hydroxy, $-N(R^{20})_2$, -O-acyl, $-N(R^{20})$acyl, $-OCOOR^{20}$, or $-OCON(R^{20})_2$;

R^{33} is aryl or heteroaryl, with the proviso that when R^{33} is heteroaryl, the $CO-R^{33}$ bond is to a carbon atom in the R^{33} group;

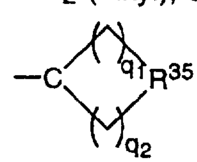
R^{34} is alkyl, cycloalkyl or aryl and in addition R^{34} may also be H when R^1 and R^{21} together with the carbon atom to which they are attached form a saturated heterocyclic ring containing 3 to 7 carbon atoms and two groups independently selected from S, O, and $N-R^{20}$;

R^{35} is $-CH_2-$, $-NR^{20}-$ or -O-;

R^{36} is $-NH_2$, alkyl or alkoxy;

R^{37} is independently selected from the group consisting of H and alkyl;

R^{38} is $-CO-(CH_2)_{0-5}-OR^5$, $-SO_2$-(alkyl), or



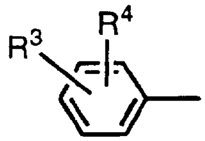
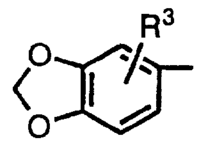
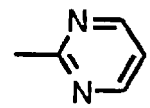
wherein q_1 and q_2 are independently 1-5, provided that the sum of q_1 and q_2 is 2-5; and

R^{39} and R^{40} are independently selected from the group consisting of =O and (H,H).

In a preferred group of compounds Y and Z are N.

In another preferred group of compounds Y is CH and Z is N.

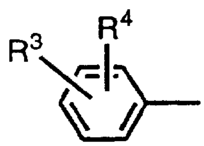
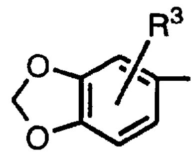
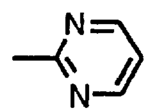
In another preferred group of compounds R is


, 
, or 

and X is O, SO, SO_2, CH_2, CH(alkyl), $C(alkyl)_2$, -CH(OH)-, or -$N(R^{20})CO$.

In another preferred group of compounds R^3 and R^4 are H and either R^1 is cycloalkyl, or alkyl, and R^{21} is H or R^1 and R^{21} together form =O.

In another preferred group of compounds R is

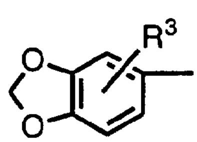
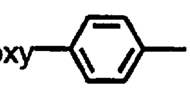

, 
, or 
,

X is O ,SO, SO_2, CH_2, CH(alkyl), $C(alkyl)_2$, or -$N(R^{20})CO$; R^3 and R^4 are H and either R^1 is cycloalkyl or alkyl; and R^{21} is H or R^1 and R^{21} together form =O or  .

In another preferred group of compounds at least one of R^{27} and R^{28} is alkyl.

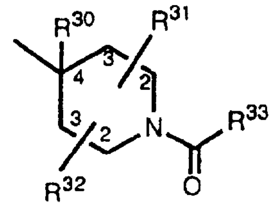
In another preferred group of compound one of R^{27} or R^{28} is methyl and the other is hydrogen.

In another preferred group of compounds R is

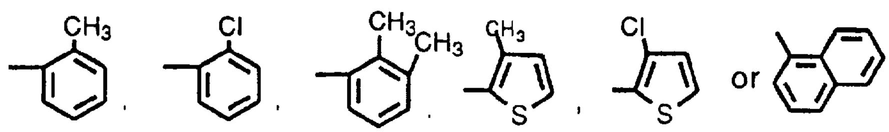

or alkoxy .

In another preferred group of compounds X is SO_2, CH_2, or -$N(CH_3)$-CO-.

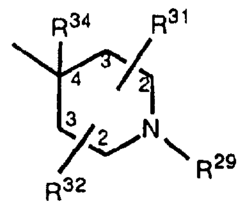
In another group of preferred compounds, R^2 has the formula



and R^{30} is H or CH_3: R^{31} and R^{32} are H: and R^{33} is ortho-substituted aryl or heteroaryl, preferably



In another group of preferred compounds, R^2 has the formula



R^{34} is methyl and R^{31} and R^{32} are H.

Preferred specific compounds of this invention are listed hereinafter as compound numbers: 17, 18,25, 30, 31, 32, 34, 35, 36, 37, 41, 43, 44, 49, 53, 54, 56, 57, 58, 59, 80, 82, 84, 85, 94, 98, 100, 108, 121, 126, 127, 137, 145, 151, 152, 154, 155, 162, 166, 178, 179, 181, 185, 190, 191, 194, 199, 214, 215, 216, 225, 247, 253, 256, 257, 337, 339, 340, 341, 349, 351, 367, 409, 459, 479, 488, 489, 490, 500, 501, 502, 503, 505, 506, 507, 515, 516, 517, 555, 562.

Another aspect of the invention is a pharmaceutical composition which comprises a compound having structural formula I as defined above in combination with a pharmaceutically acceptable carrier.

Another aspect of the invention is the use of a compound formula I for the preparation of a pharmaceutical composition useful in the treatment of cognitive disorders and neurodegenerative diseases such as Alzheimer's disease.

Yet another aspect of the invention comprises a method for making a pharmaceutical composition comprising mixing a compound of formula I with a pharmaceutically acceptable carrier.

Another aspect of this invention is a method for treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a compound of formula I.

Another aspect of this invention is a method for treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a combination of a compound of formula I with an acetycholinesterase inhibitor.

Another aspect of this invention is a kit comprising in separate containers in a single package pharmaceutical compounds for use in combination to treat cognitive disorders in one container a compound of formula I in a pharmaceutically acceptable carrier and in a second container an acetylcholinesterase inhibitor in a pharmaceutically acceptable carrier, the combined quantities being an effective amount.

DETAILED DESCRIPTION

Except where stated otherwise the following definitions apply throughout the present specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms. Hence the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "alkoxy", "haloalkyl", etc.

Alkyl represents a straight or branched saturated hydrocarbon chain having 1 to 20 carbon atoms, more preferably 1 to 8 carbon atoms.

Alkenyl represents a straight or branched hydrocarbon chain of from 2 to 15 carbon atoms, more preferably 2 to 12 carbon atoms, having at least one carbon-to-carbon double bond.

Alkynyl represents a straight or branched hydrocarbon chain of from 2 to 10 carbon atoms, more preferably 2 to 8 carbon atoms, having at least one carbon-to-carbon triple bond.

Cycloalkyl represents a saturated carbocyclic ring having 3 to 12 carbon atoms.

Cycloalkenyl represents a carbocyclic ring having from 5 to 8 carbon atoms and at least one carbon-to-carbon double bond in the ring.

Bicycloalkyl represents a saturated bridged carbocyclic ring having 5 to 12 carbon atoms.

Acyl represents a radical of a carboxylic acid having the formula alkyl-CO-, aryl-CO-, aralkyl-CO-, cycloalkyl-CO-, alkylcycloalkyl-CO-, and heteroaryl-CO-.

Halo represents fluoro, chloro, bromo or iodo.

Aryl represents phenyl or naphthyl optionally substituted with 1 to 5 R^3 groups.

Heteroaryl represents a cyclic group of 5 or 6 atoms, or a bicyclic group of 9 or 10 atoms, at least one of which is carbon and having at least one O, S, or N atom interrupting a carbocyclic ring having a sufficient number of pi electrons to provide aromatic character. Carbon atoms may optionally be substitiuted by R^3 groups. Nitrogen atoms may optionally be substituted $-R^{20}$ or $-COR^{20}$ groups. Preferred heteroaromatic groups are pyridyl, furanyl, benzofuranyl, thienyl, benzothienyl, thiazolyl, thiadiazolyl, imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, 1,3,5-triazinyl, and indolyl.

Polyhalo represents substitution of at least 2 halo atoms to the group modified by the term "polyhalo".

Hydroxyamidino represents a group having the formula

$$NH_2\text{-}\overset{|}{C}\text{=N-OH}\ .$$

Azabicyclo represents a saturated bridged ring containing from 4 to 8

carbon atoms and at least one nitrogen atom.

Sulfonyl represents a group of the formula $-SO_2-$.

Sulfinyl represents a group of the formula -SO-.

Alkylene represents a group having the formula $-(CH_2)_q$, wherein q is an integer of from 1 to 20.

Naturally occurring amino acid (NOAA) means an acid selected from the group consisting of alanine(ala), arginine (arg), asparagine (asn), aspartic acid (asp), cysteine (cys), glutamine (gln), glutamic acid (glu), glycine (gly), histadine (his), isoleucine (ile), leucine (leu), lysine (lys), methionine (met), phenylalanine (phe), proline (pro), serine (ser), threonine (thr), tryptophan (trp), tyrosine (tyr), and valine (val).

Nitrogen protecting group (Prot) means a group capable of protecting a nitrogen on a naturally occurring amino acid (or an enantiomer thereof) from reaction. Preferred nitrogen protecting groups

are carbobenzyloxy (CBZ), $CH_3OCO(CH_2)_9CO$, and t-butoxycarbonyl (BOC). Of course any operable nitrogen protecting group is included.

When a variable appears more than once in the structural formula, for example R^5 when X is $-C(OR^5)_2-$, the identity of each variable appearing more than once may be independently selected from the definition for that variable.

Compounds of this invention may exist in at least two stereo configurations based on the asymmetric carbon to which R^1 is attached, provided that R^1 and R^{21} are not identical. Further stereoisomerism is present when X is SO, or $C(OR^5)_2$ (when the two R^5 groups are not the same) or when R^{27} or R^{28} is not hydrogen. Also within formula I there are numerous other possibilities for stereoisomerism. All possible stereoisomers of formula I are within the scope of the invention.

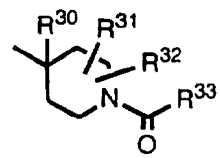
Compound of formula I can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for purposes of this invention.

A compound of formula I may form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia or sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

Compounds in accordance with formula I may be produced by processes known to those skilled in the art as shown by the following reaction steps:

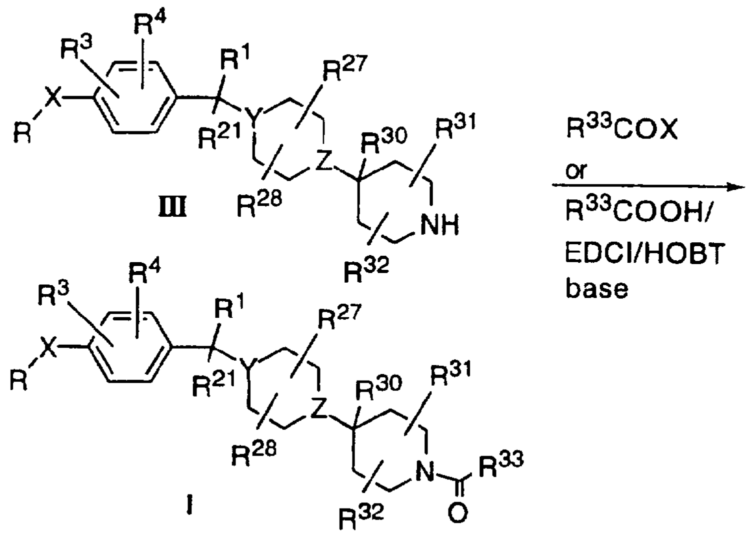
General Description of Methods:

Compounds wherein R^2 has the formula

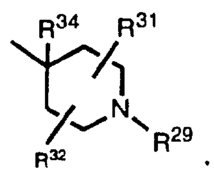


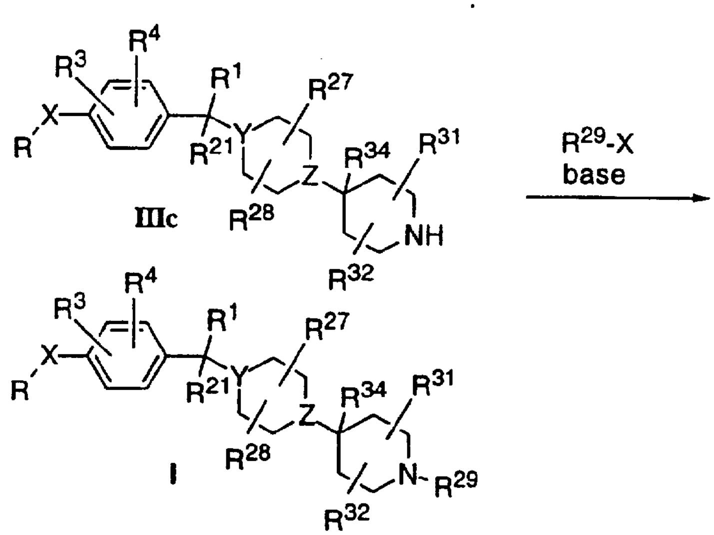
can be made as shown in Scheme I.

Scheme 1



For compounds wherein R^2 has the formula

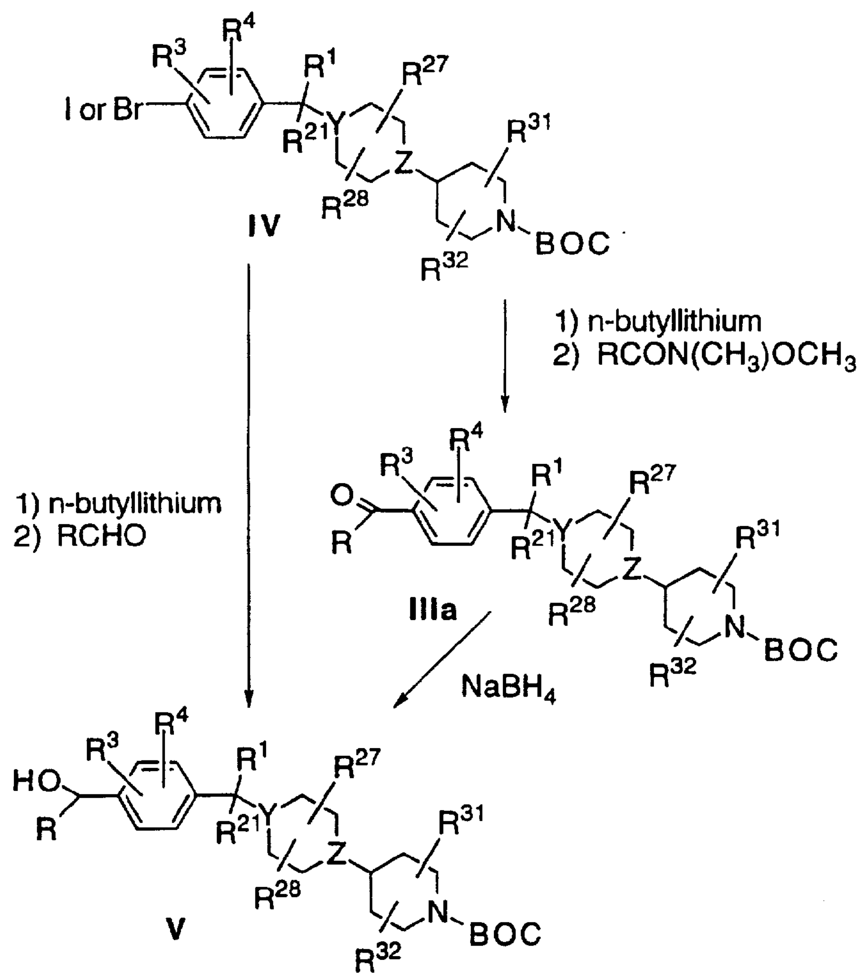


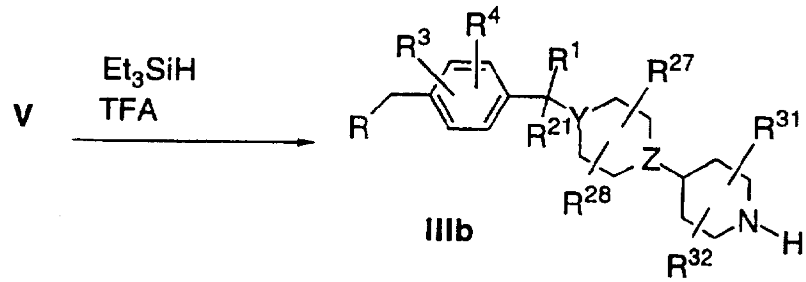


Intermediate **III** is treated with a suitably activated carboxylic acid derivative, $R_{33}CO$-X, where X is a leaving group such as halogen or $OCOCH_3$. Alternatively, a mixture of compound **III** and $R_{33}COOH$ can be treated with N-hydroxybenzotriazole and a carbodiimide such as N-ethyl-N-(3-dimethylaminopropyl)-carbodiimide hydrochloride or dicyclohexylcarbodiimide in the presence of a base such as triethylamine and a solvent such as DMF to give **I**. Alternatively, intermediate **IIIc** is treated with a group R_{29}-X, where X and R_{29} are as previously defined (except R_{29}≠H), in the presence of a base such as triethylamine.

Intermediates **III** can be made via a variety of methods. When X= CH_2 or CO, **III** can be made as shown in Scheme 2:

Scheme 2



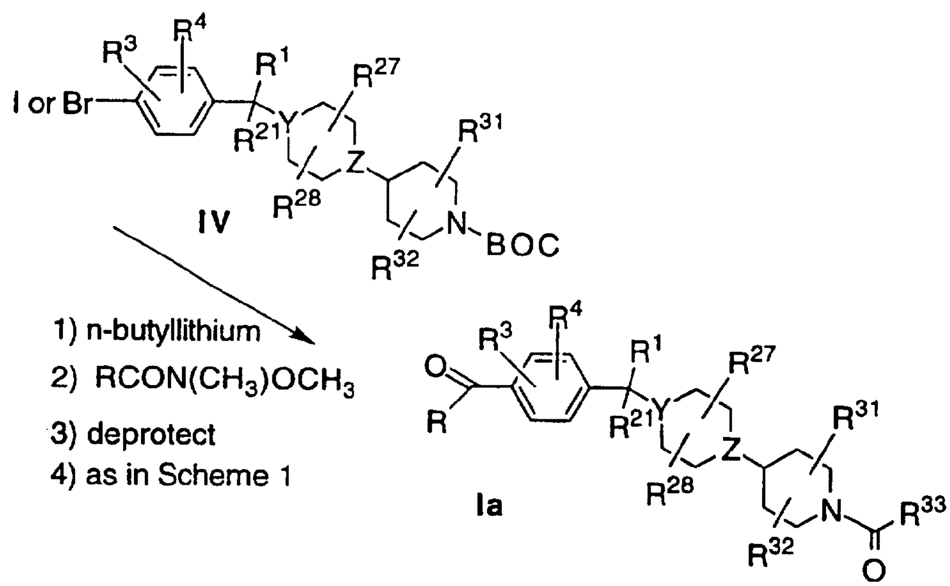


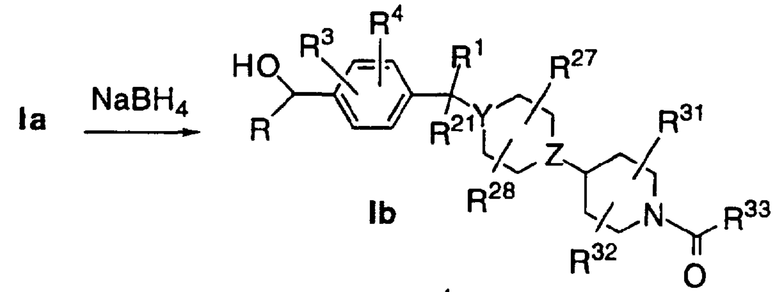
IIIb

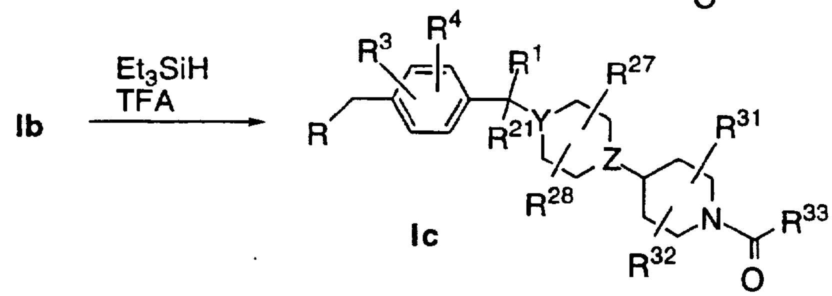
Aryl halide **IV** is treated with an alkyllithium such as n-butyllithium or t-butyllithium followed by reaction with an $RCON(CH_3)OCH_3$ to give compound **IIIa**, which can be deprotected and converted to **I** as shown above. Additionally, **IIIa** can be reduced to the alcohol **V** with a suitable reducing agent such as sodium borohydride. Compound **V** can also be made by treatment of **IV** with an alkyllithium as previously described followed by reaction with RCHO. Compound **V** is converted to compounds **IIIb** by treating **V** with a reducing agent such as triethylsilane in the presence of a strong acid such as trifluoroacetic acid.

Compounds of formula **Ia**, **Ib**, and **Ic** can be prepared via a related sequence as shown in Scheme 3:

Scheme 3



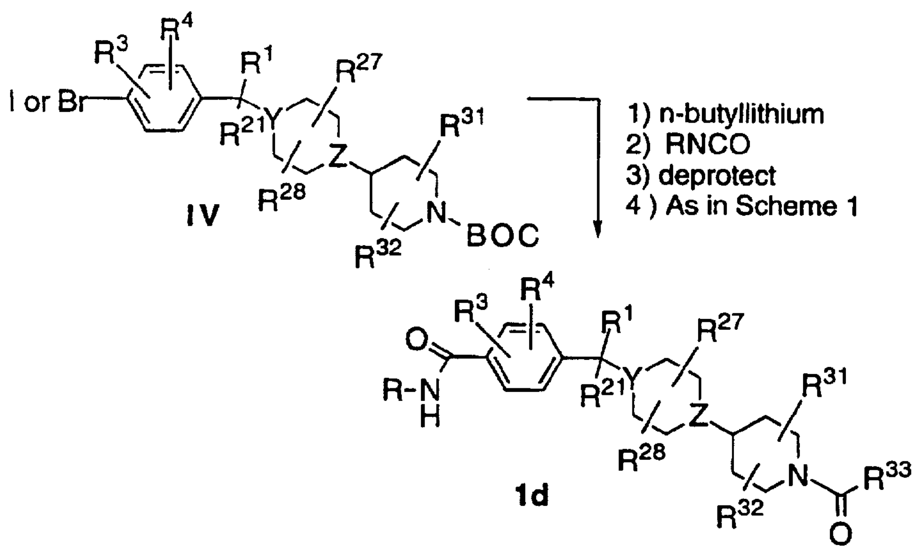


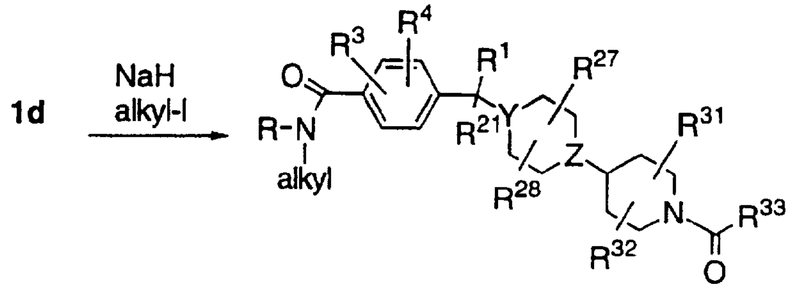


Intermediate **IIIa** is prepared as shown in Scheme 2, deprotected and then converted to **Ia** using methods of Scheme 1. This can then be converted to **Ib** and **Ic** using methods of Scheme 2.

Other compounds of this invention can be prepared by methods similar to those described in Schemes 2-3 wherein the aryl lithium reagent derived from **IV** is reacted with various electrophiles. For instance, compounds where **X** is NHCO or N(alkyl)CO can be prepared as shown in Scheme 4:

<u>Scheme 4</u>



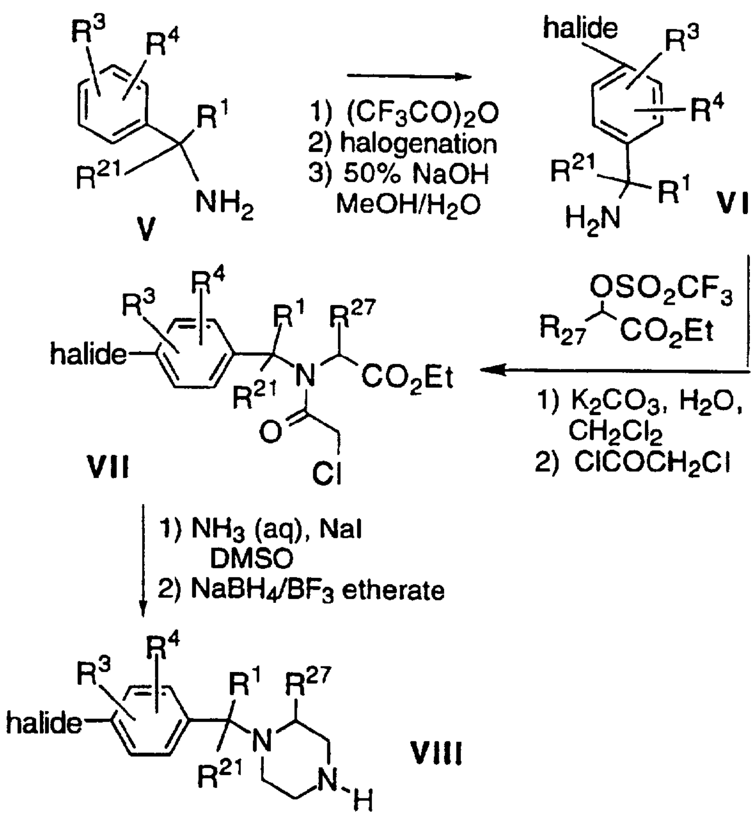


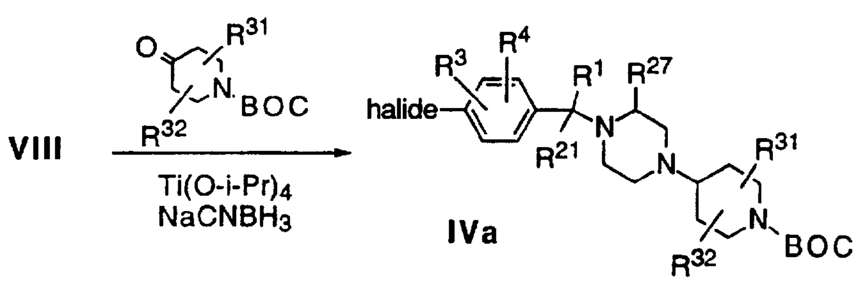
Intermediate **IV** is reacted with an alkyllithium as previously described followed by addition of an isocyanate RNCO. The intermediate is deprotected and converted to compounds of type **1d** as described in Scheme 1. Compounds of type **1d** are converted to compounds **1e** by reacting with an alkyliodide such as methyliodide in the presence of a suitable base such as sodium hydride.

Intermediate **IV** can be prepared via one of the following procedures:

<u>Scheme 5</u>

Intermediate **IVa:**

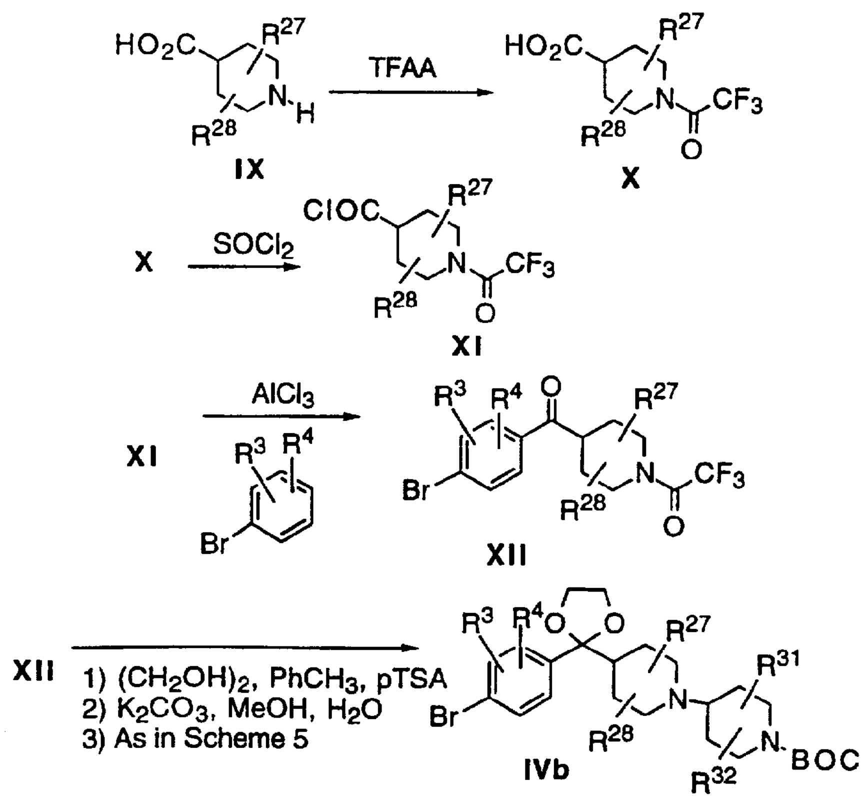




Benzylamine **V** is protected as its trifluoroacetamide, treated with a halogenating agent such as bromine, dibromodimethylhydantoin, or bis(trifluoroacetoxy)iodobenzene, and deprotected with aqueous base to give **VI**. This is treated with a carboxylic ester derivative containing a leaving group such as trifluoromethanesulfonate in the 2-position followed by chloroacetyl chloride to give **VII**. Treatment of **VII** with ammonia followed by reduction with $NaBH_4/BF_3$ etherate gives **VIII**. Treatment of **VIII** with an N-BOC 4-piperidinone derivative preferable in the presence of a Lewis acid such as titanium tetraisopropoxide followed by a reducing agent such as sodium cyanoborohydride affords **IVa**.

<u>Scheme 6</u>

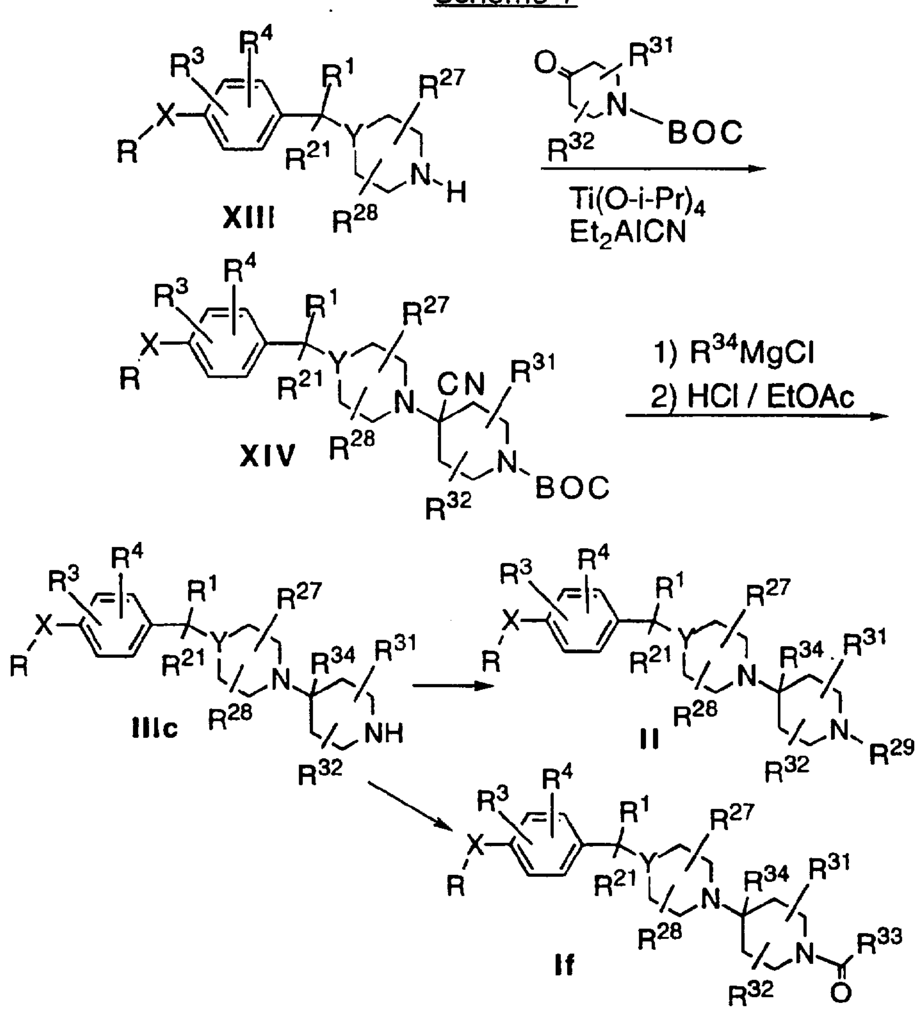
Intermediate **IVb:**



A piperidine 4-carboxylic acid derivative **IX** is protected on nitrogen using trifluoroacetic anhydride and converted to the corresponding acid chloride **XI** using thionyl chloride. Intermediate **XI** is reacted with an arylhalide in the presence of a Lewis acid such as aluminum chloride to give **XII**. The carbonyl group of **XII** is protected by treatment with ethylene glycol in the presence of a strong acid such a toluenesulfonic acid. The nitrogen is deprotected using aqueous alcoholic base, and the resulting compound treated with an N-BOC 4-piperidinone derivative as described in Scheme 5 to afford **IVb**.

Compounds of formula **If** (where $R_{30} \neq H$) and **II** are prepared as shown in Scheme 7:

Scheme 7

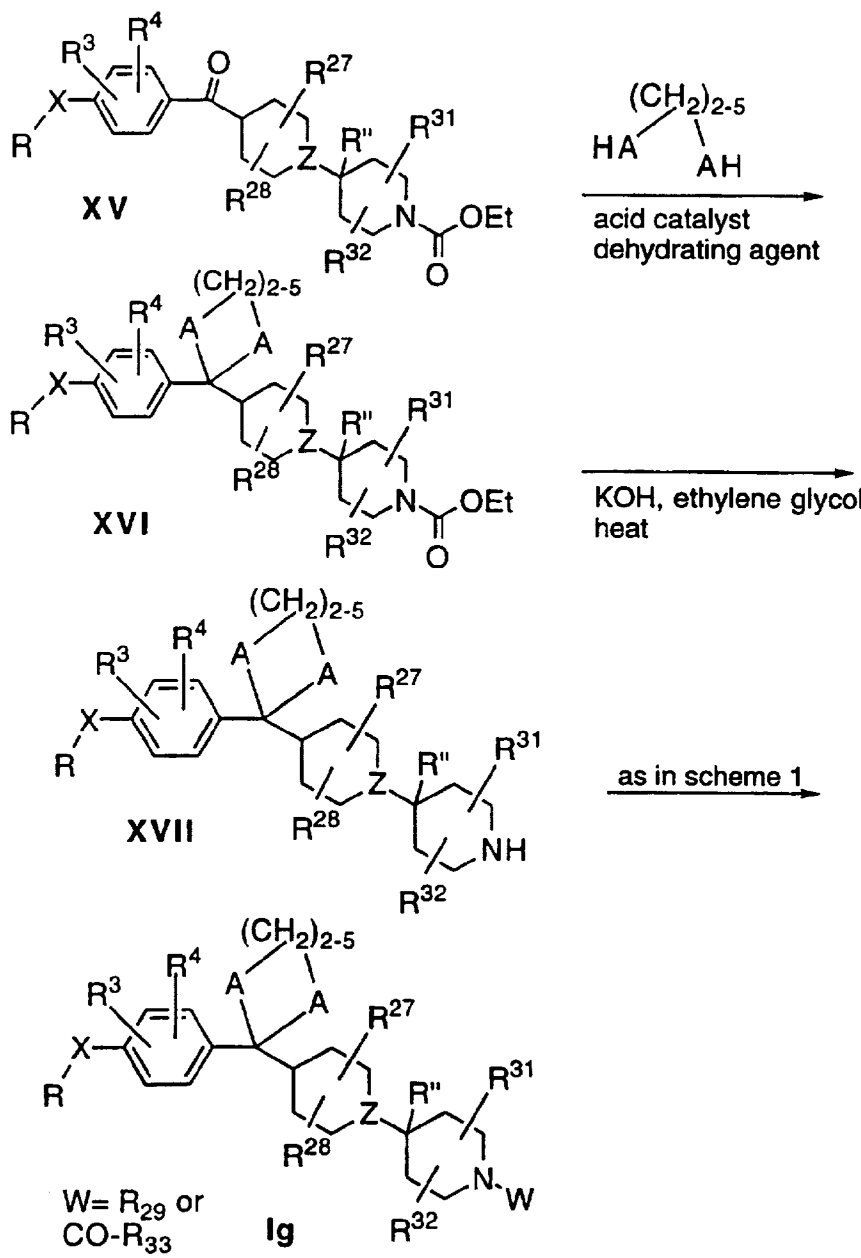


Intermediate **XIII** is treated with an N-BOC 4-piperidinone derivative preferably in the presence of a Lewis acid such as titanium

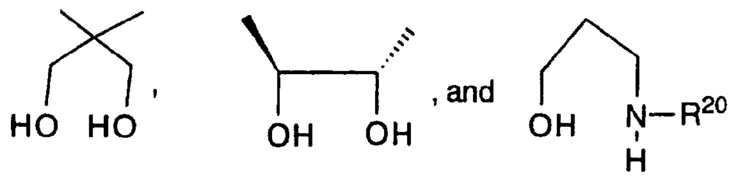
tetraisopropxide followed by treatment with diethylaluminum cyanide to give **XIV**. This is treated with Grignard reagent $R_{34}MgCl$ followed by hydrolysis with aqueous acid to give **IIIc**. Compound **IIIc** can be converted to compounds of type **If** and **II** using the method shown in Scheme 1.

In addition to methods described above, compounds of formula **Ig** (where **A** is O, S or N-R^{20}) can be prepared as described in Scheme 8.

Scheme 8



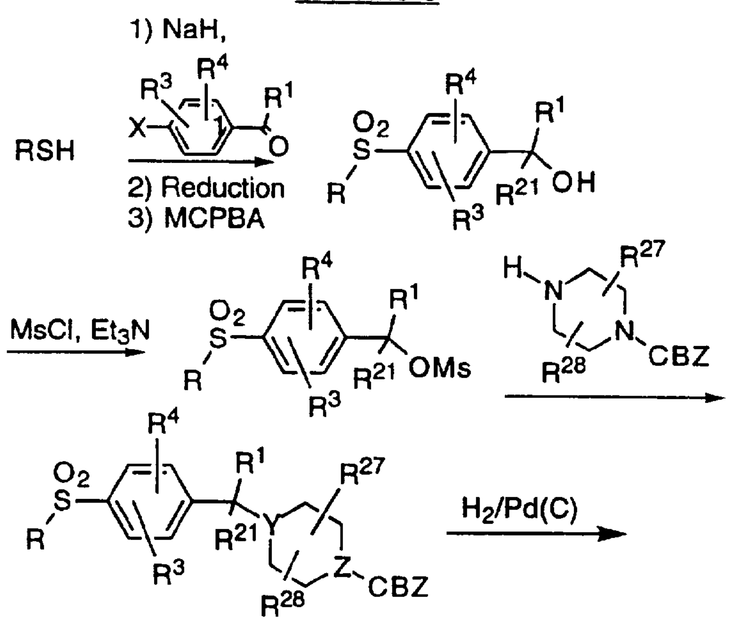
In the compound $HA-(CH_2)_{2-5}-AH$, each A is independently O, S, or $N-R_{20}$, and each CH_2 group may optionally be substituted by one or more alkyl groups. Examples of the compound $HA-(CH_2)_{2-5}-AH$, include

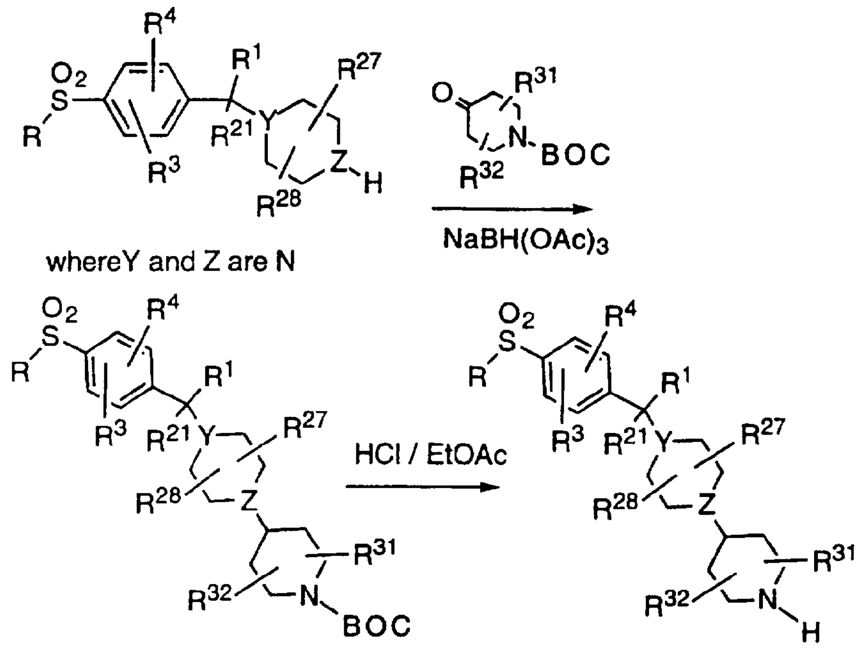


Compound **XV** (where R" is either R_{30} or R_{34}) is prepared as described in schemes 7 and 10. This is treated with $HA-(CH_2)_{2-5}-AH$ optionally in the presence of an acid catalyst and a dehydrating agent. When A is O , the acid catalyst is preferably an organic protic acid such as toluenesulfonic acid and the dehydrating agent is triethyl orthoformate. When A is S, a Lewis acid such as boron trifluoride etherate serves as both acid catalyst and dehydrating agent. The resulting product **XVI** is hydrolyzed with a strong base such as potassium hydroxide to give **XVII.** This is converted to to **Ie** via methods described in scheme 1.

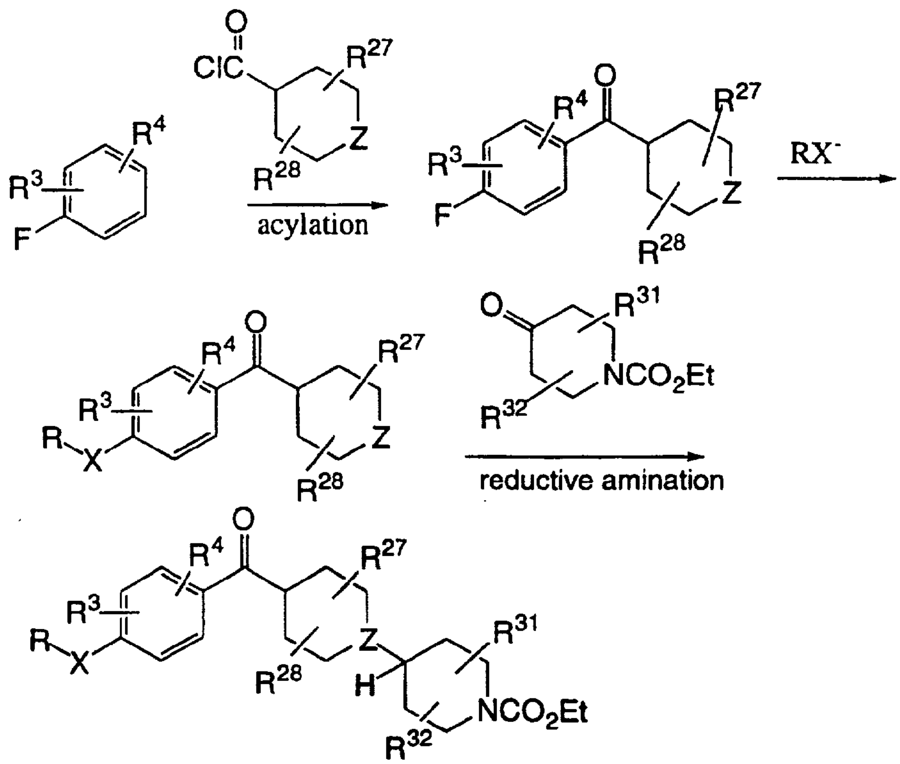
When X= S, SO, or SO_2, intermediates **III** are prepared as shown in the following schemes:

Scheme 9





Scheme 10



The above reactions may be followed if necessary or desired by one or more of the following steps; (a) removing any protective groups

from the compound so produced; (b) converting the compound so-produced to a pharmaceutically acceptable salt, ester and/or solvate; (c) converting a compound in accordance with formula I so produced to another compound in accordance with formula I, and (d) isolating a compound of formula I, including separating stereoisomers of formula I.

Based on the foregoing reaction sequence, those skilled in the art will be able to select starting materials needed to produce any compound in accordance with formula I.

In the above processes it is sometimes desirable and/or necessary to protect certain groups during the reactions. Conventional protecting groups, familiar to those skilled in the art, are operable. After the reaction or reactions, the protecting groups may be removed by standard procedures.

The compounds of formula I exhibit selective m2 and/or m4 muscarinic antagonizing activity, which has been correlated with pharmaceutical activity for treating cognitive disorders such as Alzheimers disease and senile dementia.

The compounds of formula I display pharmacological activity in test procedures designated to indicate m1 and m2 muscarinic antagonist activity. The compounds are non-toxic at pharmaceutically therapeutic doses. Following are descriptions of the test procedures.

MUSCARINIC BINDING ACTIVITY

The compound of interest is tested for its ability to inhibit binding to the cloned human m1, m2, m3, and m4 muscarinic receptor subtypes. The sources of receptors in these studies were membranes from stably transfected CHO cell lines which were expressing each of the receptor subtypes. Following growth, the cells were pelleted and subsequently homogenized using a Polytron in 50 volumes cold 10 mM Na/K phosphate buffer, pH 7.4 (Buffer B). The homgenates were centrifuged at 40,000 x g for 20 minutes at 4°C. The resulting supernatants were discarded and the pellets were resuspended in Buffer B at a final concentration of 20 mg wet tissue/ml. These membranes were stored at -80°C until utilized in the binding assays described below.

Binding to the cloned human muscarinic receptors was performed using ^{3}H-quinuclidinyl benzilate (QNB) (Watson et al., 1986). Briefly, membranes (approximately 8, 20, and 14 μg of protein assay for the m1, m2, and m4 containing membranes, respectively) were incubated with ^{3}H-QNB (final concentration of 100-200 pM) and increasing concentrations of unlabeled drug in a final volume of 2 ml at 25°C for 90 minutes. Non-specific binding was assayed in the presence of 1 μM atropine. The incubations were terminated by vacuum filtration over GF/B glass fiber filters using a Skatron filtration apparatus and the filters were washed with cold 10mM Na/K phosphate butter, pH 7.4. Scintillation cocktail was added to the filters and the vials were incubated overnight. The bound radioligand was quantified in a liquid scintillation counter (50% efficiency). The resulting data were analyzed for IC_{50} values (i.e. the concentration of compound required to inhibit binding by 50%) using the EBDA computer program (McPherson, 1985). Affinity values (K_i) were then determined using the following formula (Cheng and Prusoff, 1973);

$$K_i = \frac{IC_{50}}{1+\left[\dfrac{\text{concentration of radioligand}}{\text{affinity } (K_D) \text{ of radioligand}}\right]}$$

Hence, a lower value of K_i indicates greater binding affinity.

To determine the degree of selectivity of a compound for binding the m2 receptor, the K_i value for m1 receptors was divided by the K_i value for m2 receptors. A higher ratio indicates a greater selectivity for binding the m2 muscarinic receptor.

RESULTS OF THE TESTS

Compound No.	Ki (nM) m1	m2	m4
17	47.33	0.14	2.26
18	48.37	0.11	0.77
25	337.68	0.55	6.51
31	308.95	0.63	12.10
41	29.9	0.06	1.47
44	36.79	0.11	0.76

84	12.32	0.04	0.06
94	28.99	0.02	0.76
100	6497	0.12	3.38
554	0.81	0.01	0.04
590	29.33	0.03	0.80

For the compounds appearing in the TABLE OF COMPOUNDS the following range of muscarinic antagonistic activity was observed

m2: 0.01 nM to 106 nM

m1: 0.24 nM to 1900 nM

m4: 0.02 nM to 705 nM

For preparing pharmaceutical compositions from the compounds of formula I, compounds capable of enhancing ACh release, and ACh'ase inhibitors, pharmaceutically acceptable, inert carriers are admixed with the active compounds. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as dilutents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it may also be an encapsulating material.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parentertal administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit.

The invention also contemplates alternative delivery systems including, but not necessarily limited to, transdermal delivery. The transdermal compositions can take the form of creams, lotions and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active components. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation such as packeted tablets, capsules and powders in vials or ampules. The unit dosage form can also be a capsule, cachet or tablet itself, or it may be the appropriate number of any of these in a packaged form.

The quantity of active compound in a unit dose preparation may be varied or adjusted from 1 mg to 100 mg according to the particular application and the potency of the active ingredient and the intended treatment. This would correspond to a dose of about 0.001 to about 20 mg/kg which may be divided over 1 to 3 administrations per day. The composition may, if desired, also contain other therapeutic agents.

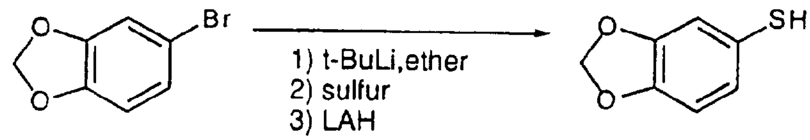
The dosages may be varied depending on the requirement of the patient, the severity of the condition being treating and the particular compound being employed. Determination of the proper dosage for a particular situation is within the skill of those in the medical art. For convenience, the total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery. When a compound of formula I or a compound capable of enhancing ACh release is used in combination with an acetylcholinesterase inhibitor to treat cognitive disorders these two active components may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising a compound of formula I or a compound capable of enhancing ACh release and an acetylcholinesterase inhibitor in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional oral or parenteral dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the acetylcholinesterase inhibitor may range from 0.001 to 100 mg/kg body weight.

The invention disclosed herein is exemplified by the following preparation and examples which should not be construed to limit the

scope of the disclosure. Alternative mechanistic pathways and analogous structures may be apparent to those skilled in the art.

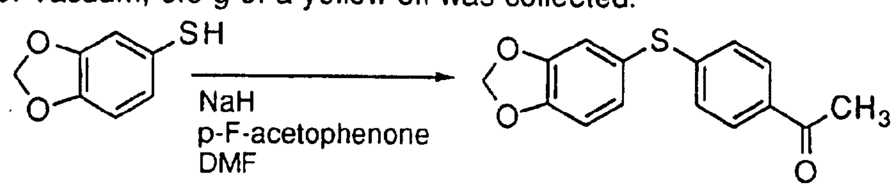
In the following examples intermediate numerals have normal type and are enclosed by parenthesis, e.g., (5). Product compounds are in bold type and underlined, e.g., **5**

Example 1: Synthesis of Compound No. 4



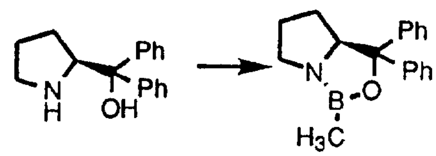
An ether (650 ml) solution of the bromide (15.5 g, 0.07 mol) was cooled in a dry ice acetone bath where t-BuLi (100 ml, 1.7 M) was added dropwise. After stirring for 3h, the sulfur powder (4.9 g, 0.15 mol) was added and stirring continued for an additional hour. The temperature was warmed to room temperature and stirring continued for 16h. After quenching with water, ether (Et_2O) was added and the organic phase was washed with 5% HCl, water, 10% Na_2CO_3 and then brine. The solution was concentrated and purified by chromatography with 5% ethyl acetate (EtOAc) / hexane (R_f = 0.7/ CH_2Cl_2: hexane 1:1) with 33 g yellow solid collected.

The sample was dissolved in THF (50 mL) and cooled in an ice water bath where it was added to a mixture of LAH (0.91g, 0.02 mol) and 20 mL THF. Stirring was continued for 10 minutes, then warmed to room temperature and stirred for 1h. The reaction was diluted with EtOAc and quenched with water. 10% HCl was added and the organic layer separated, washed with water and brine. After concentration and drying under vacuum, 6.6 g of a yellow oil was collected.

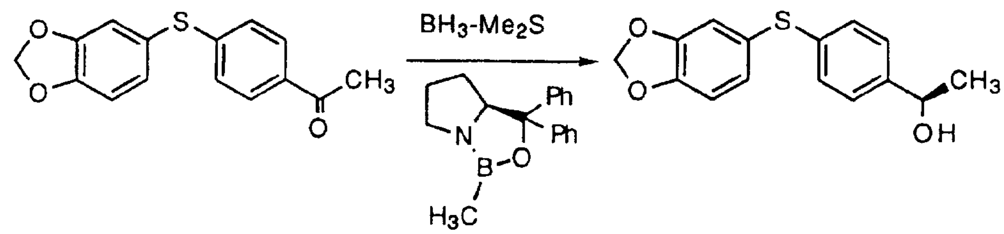


The thiol (19 g, 124 mmol) was dissolved in DMF (180 ml) and cooled in an ice bath where NaH (4.9 g, 60% in oil) was added in portions. Stirring was continued for 1h, then warmed to room temperature and stirred for an additional 1h. The 4-fluoroacetophenone (18.7 g, 136 mmol) was added dropwise and then stirred at 70°C for 3h. The reaction was concentrated on a rotovap, diluted with EtOAc, and washed with

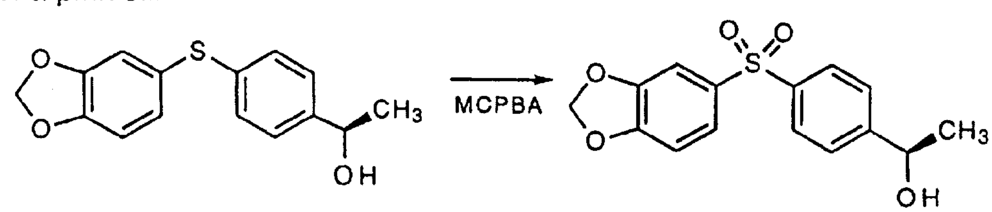
water and brine. The solution was evaporated on a rotovap and the residue chromatographed on silica gel (20% EtOAc/hexane) to collect 24.5g (73%) of a pale yellow solid.



To a solution of the alcohol (10.1 g,40 mmol) in toluene (100mL) was slowly added the trimethyl boroxine (3.3 g, 27 mmol). After 4h, the volatiles were removed by distillation (oil bath temp=140-150°C). Cooling to room temperature was followed by addition of toluene (50mL), and removal of the volatiles by distillation (repeat again). The residue was placed under high vacuum and the flask heated to 150°C. After drying under vacuum overnight the off white solid was dissolved in THF (100ml) and used without further purification.

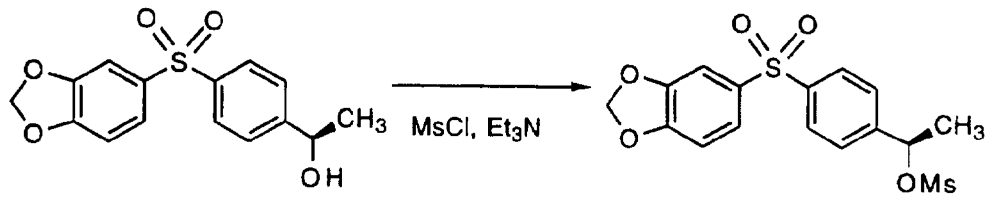


The ketone (36 g, 133 mmol) was dissolved in THF (200 ml), followed by addition of the catalyst (8.8 g in 80 ml THF). $BH_3(CH_3)_2S$ (42 ml, 2mol/L in THF) was added dropwise, and the reaction stirred for 30min. CH_3OH (200mL) was added and the solution concentrated. The residue was dissolved in EtOAc and washed with water and brine. The solution was dried over Na_2SO_4, filtered and concentrated to give 40.3 g of a pink oil.

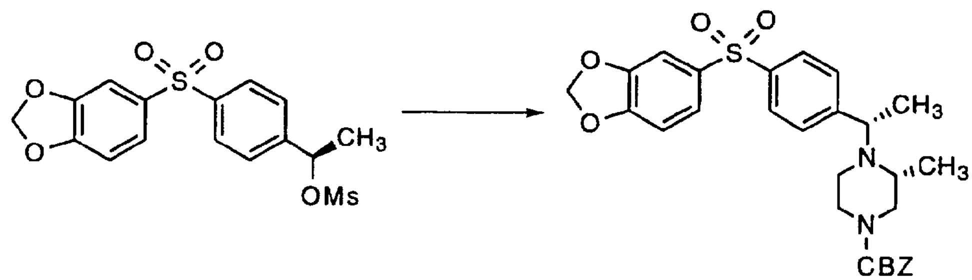


A CH_2Cl_2 (600 ml) solution of the sulfide (40.3g, 147mmol) was cooled in an ice water bath where MCPBA (79.7 g, 70%) was added in portions. After stirring for 1h the temperature was warmed to room temperature and stirred for 4h. After diluting with CH_2Cl_2, the reaction

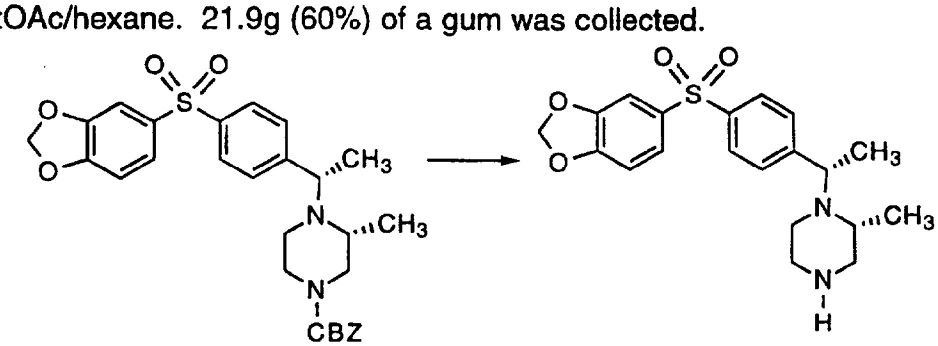
was washed with 10%Na_2CO_3, water, and brine. The solution was dried over, Na_2SO_4, filtered and concentrated to collect 42.5g of an off white solid.



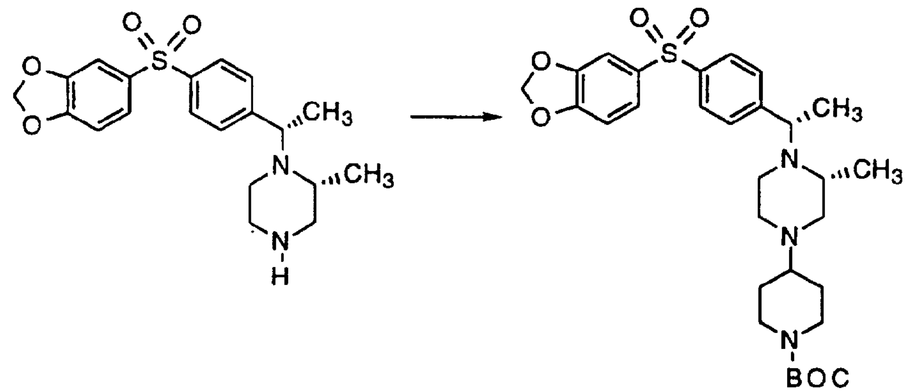
A CH_2Cl_2 (250 ml) solution of the alcohol (21.4 g, 70 mmol) and triethyl amine (Et_3N) (19.5 ml) was cooled in an ice water bath where methanesulfonyl chloride (6.5 ml) were added dropwise. After 1h the reaction was diluted with CH_2Cl_2 and washed with 2% HCl, water, saturated $NaHCO_3$, water, brine, and dried over Na_2SO_4. Filtration and concentration gave 27g of an oil which was used without further purification.



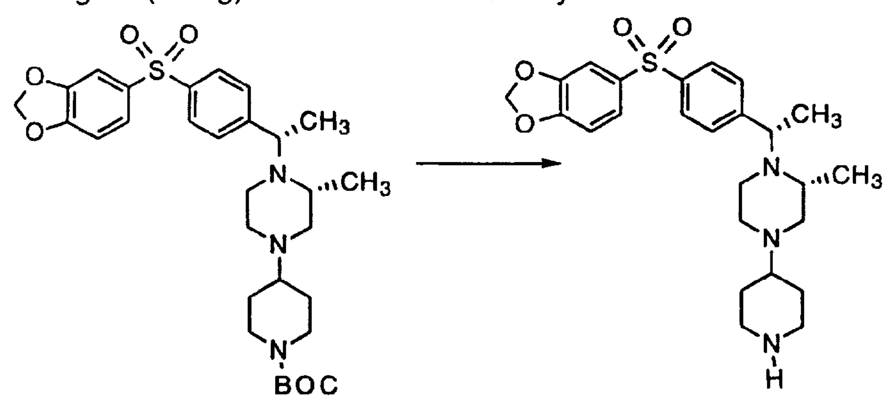
A mixture of the mesylate (made from 21.4 g alcohol), piperazine (18 g, 0.07 mol), and 2,2,6,6-tetramethyl piperidine (11.8 g, 0.084 mol) was stirred in CH_3CN (200 ml) at reflux overnight. After cooling to room temperature the CH_3CN was removed on a roto vap and replaced with EtOAc. The solution was washed with 10% Na_2CO_3, and water. After concentration the residue was chromatographed on silica gel using 1:3 EtOAc/hexane. 21.9g (60%) of a gum was collected.



A mixture of the CBZ amine (10.3g, 19.6 mmol), 100 ml water, CH_3OH (100 ml), and 100 ml conc. HCl was heated in an oil bath at 100°C for 5h. The mixture was cooled in an ice bath and 50% NaOH was added until the pH=9. EtOAc was added, followed by separation and washing with water. The organic solution was concentrated and the residue chromatographed on silica gel (CH_2Cl_2:CH_3OH 50:1, saturated with NH_4OH solution). The product was collected in 86% as a heavy oil.

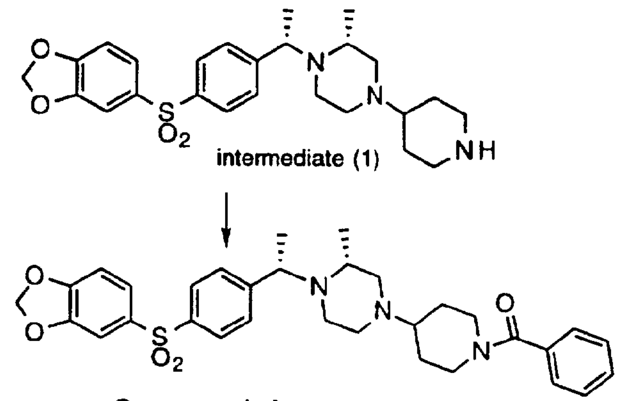


The amine (1.0 g, 2.5 mmol), N-BOC piperidinone (0.5 g, 2.5 mmol), and HOAc (0.15 ml) were dissolved in CH_2Cl_2 (20 ml). NaBH $(OAc)_3$
(0.55 g, 3.8 mmol) was added in several portions and the solution stirred overnight. CH_2Cl_2 was added and washed with saturated $NaHCO_3$, water and brine. The solution was dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed using EtOAc. A colorless gum (0.96g) was obtained in 65% yield.



The N-BOC compound (0.87 g, 1.5 mmol) was dissolved in EtOAc (20 ml), and 6N HCl (3.5 ml) was added with stirring. After 2h, CH_2Cl_2 was added and the solution was washed with saturated $NaHCO_3$, and

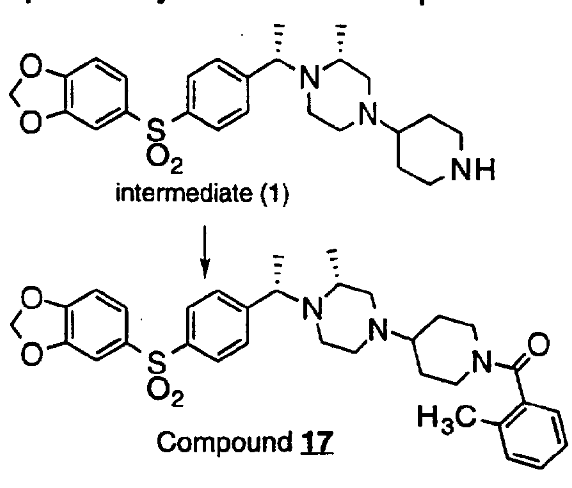
dried over Na_2SO_4. After filtration the solution was concentrated and dried under vacuum to give a white powder (0.6g, 85%).



Compound 4

Stir for 20h. at RT a solution of intermediate (1) (0.025 g), N-hydroxybenzotriazole (HOBT) (0.01 g), benzoic acid (0.0125 g), Et_3N (0.01 mL) and N-ethyl-N-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) (0.025 g) in DMF (0.3 ml). Dilute with EtOAc, wash with water and with $NaHCO_3$ solution, dry over $MgSO_4$ and filter through a small plug of silica gel, washing with EtOAc. Evaporate to obtain the free base form of the title compound. Dissolve this in CH_2Cl_2 (0.2 mL) and add to a solution of HCl in dioxane (4M; 0.1 mL) in Et_2O (1.5 mL). Stir for 5 min., centrifuge, wash by suspension and centrifugation 3x with Et_2O and dry at RT in a stream of N_2, then at high vacuum to obtain the dihydrochloride. Mp: 215-225°C, with decomposition; Mass spectrum: MH+ = 574.

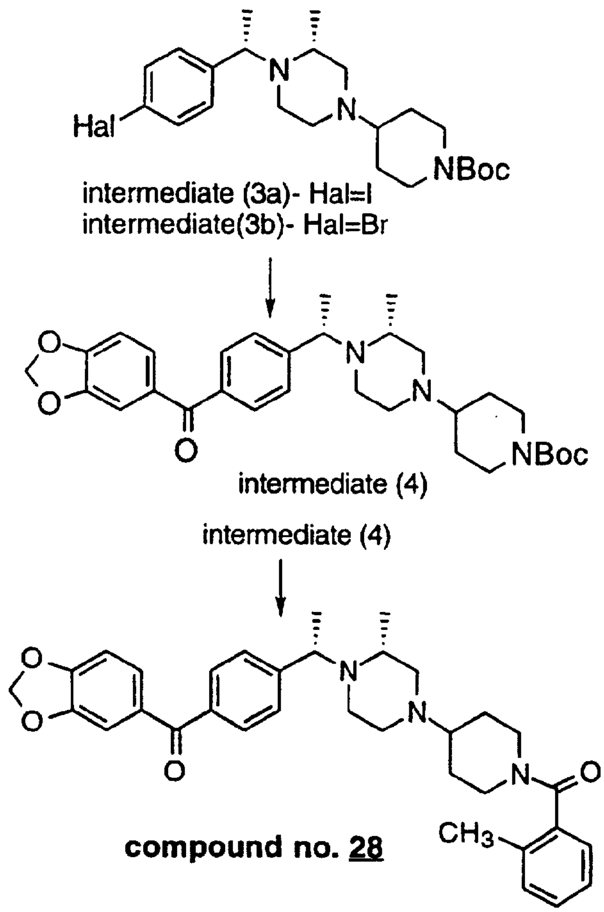
Example 2: Synthesis of Compound No. 17



Compound 17

Stir for 20h. a mixture of intermediate (1) from example 1, (0.05 g), CH_2Cl_2 (1.5 ml), o-toluoyl chloride (0.1 ml) and 1N aq. NaOH (2 ml). Separate the organic phase, dry and evaporate. Purify by preparative tlc, eluting with 5% CH_3OH-CH_2Cl_2. Extract the major band with 50% CH_3OH-CH_2Cl_2 and evaporate. Precipitate, wash and dry the hydrochloride (yield = 0.065 g) in the manner described in the foregoing preparation. Mp: 182-190°C with decomposition; Mass spectrum: MH+ = 588.

Example 3: Synthesis of Compound No. 28



intermediate (3a)- Hal=I
intermediate(3b)- Hal=Br

intermediate (4)

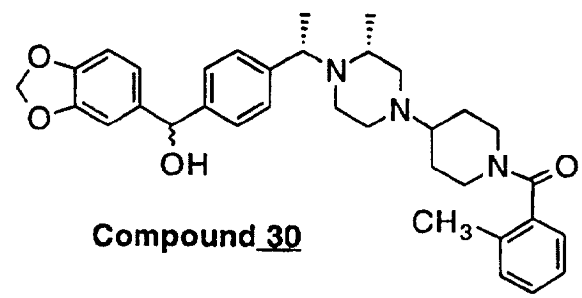
intermediate (4)

compound no. 28

This synthesis can be carried out using either intermediate (3a) or (3b) produced as shown in examples 10 and 11. To a solution of (3b) (1.86 g) in dry THF (30 ml) at -70°C under N_2 add n-BuLi (2.5 M in hexanes; 1.6 ml), stir for 10 min. and add a solution of N-piperonoyl-N,O-dimethyl-hydroxylamine (0.83 g) in THF (1 ml). Stir without cooling for 2h., add EtOAc, wash with water , dry ($MgSO_4$) and evaporate.

Chromatograph on silica gel with EtOAc-CH_2Cl_2 to obtain the major component intermediate (4) as a thick oil (1.21 g). Stir a solution of (4) (0.4 g) in EtOAc (24 ml) and conc. HCl (4.5 ml) at RT for 3h. Dilute with EtOAc, and wash with excess 1N NaOH solution. Extract with EtOAc, wash with saturated brine, dry and evaporate to obtain the NH compound. Dissolve this in CH_2Cl_2 (10 ml), and stir for 20h. at RT with o-toluoyl chloride (0.15 g) and NaOH (0.8 g) in H_2O (10 ml). Extract with CH_2Cl_2, dry ($MgSO_4$), evaporate and chromatograph on silica gel with 4% CH_3OH-CH_2Cl_2. Evaporate the pure fractions to obtain the free base as a foam (0.33 g) Dissolve a small portion this in CH_2Cl_2 and precipitate the hydrochloride salt as described in previous preparations. M.p.: 200-210°C, with decomposition; Mass spectrum: MH+ = 554

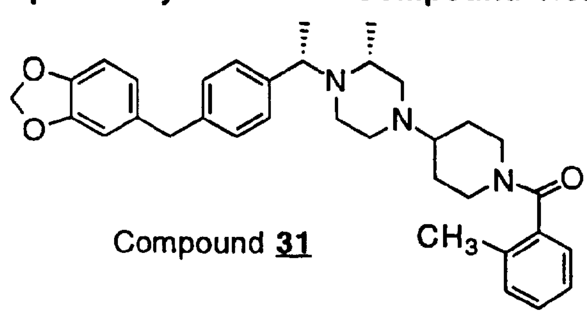
Example 4: Synthesis of Compound No. 30



Compound 30

Stir a solution of the product of example 3 (0.31 g), ethanol (15 ml) and sodium borohydride (0.042 g) at RT for 3h. Evaporate, add water, extract with EtOAc, dry, evaporate and chromatograph on silica gel with 10% CH_3OH-CH_2Cl_2 to obtain the product (0.28 g) as a white foam, a mixture of diastereoisomers. Mp: 85-95°C; Mass spectrum: MH+ = 556.

Example 5: Synthesis of Compound No. 31

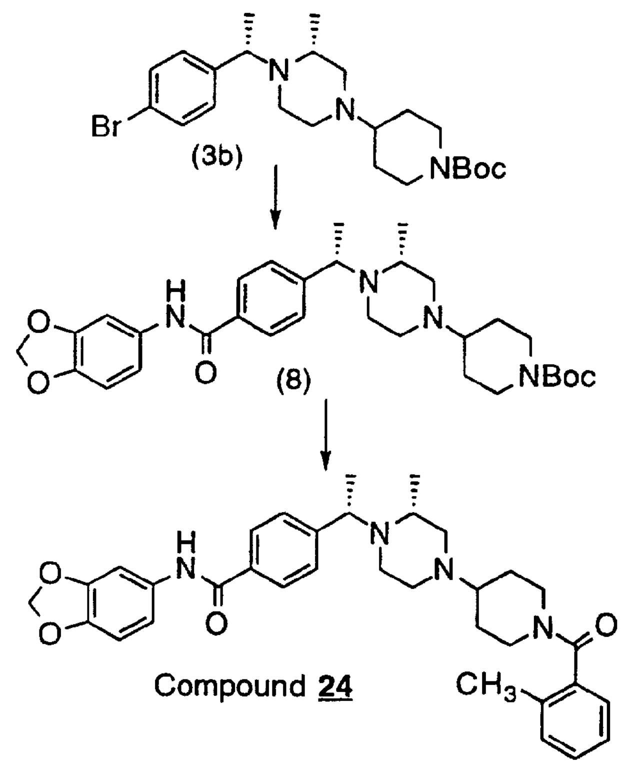


Compound **31**

Stir a solution of the product of example 4 (0.1 g) in CH_2Cl_2 (3 ml) and add triethylsilane (0.3 mL) and trifluoroacetic acid (0.12 mL). Stir at

RT for 72h. Add excess 1N NaOH solution, extract with EtOAc, dry, evaporate and purify by preparative tlc on silica plates, eluting with 5% CH_3OH-CH_2Cl_2. Remove and extract the major band, evaporate the eluate, and convert to the hydrochloride in the usual manner, to obtain a white powder (0.08 g). Mp: 210-215°C, with decomposition; Mass spectrum: MH+ = 540.

Example 6: Preparation of Compound No. 24



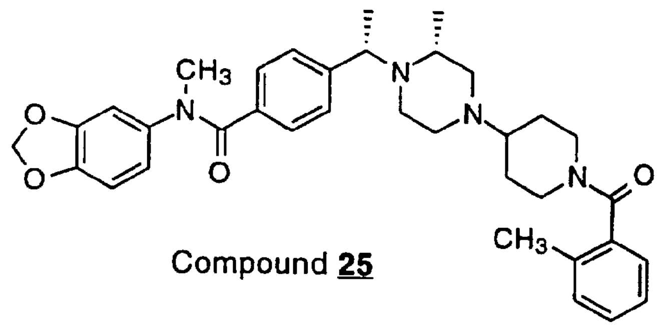
To a solution of (3b) (Example 10) (1.38 g) in dry THF (20 ml) at -70°C under dry N_2 add n-BuLi (2.5M in hexanes; 1.7 ml). Stir for 5 min., and add a solution of 3,4-methylenedioxyphenyl isocyanate (crude product, prepared by heating the corresponding acyl azide in toluene) (0.68 g) in THF (5 ml). Stir for 30 min without cooling, and work up in EtOAc-aq.$NaHCO_3$, dry ($MgSO_4$) and evaporate. Isolate the desired compound
(R_f = 0.4 in 5% CH_3OH-CH_2Cl_2) by column chromatography on silica gel, and evaporate to a pale brown foam (0.54 g).

Convert a small portion to the HCl salt in the previously described manner.

Mp: 240-250°C, with decomposition; Mass spectrum: MH+ = 551.

Stir a mixture of free base (8) (0.5 g), EtOAc (5 mL) and conc. HCl (3 ml) at RT for 2h. Add excess aq.NaOH, extract with CH_2Cl_2, dry and evaporate to a foam (0.35 g). Dissolve 0.12 g of this in CH_2Cl_2 (4 ml) and stir for 2h. at RT with 1N-NaOH (5 ml) and o-toluoyl chloride (0.05 mL). Separate and evaporate the organic phase, and isolate the product by preparative tlc on silica with 5% CH_3OH-CH_2Cl_2. Convert a small portion to the hydrochloride in the usual way. Mp: 220-230°C, with decomposition; Mass spectrum: MH+ = 569.

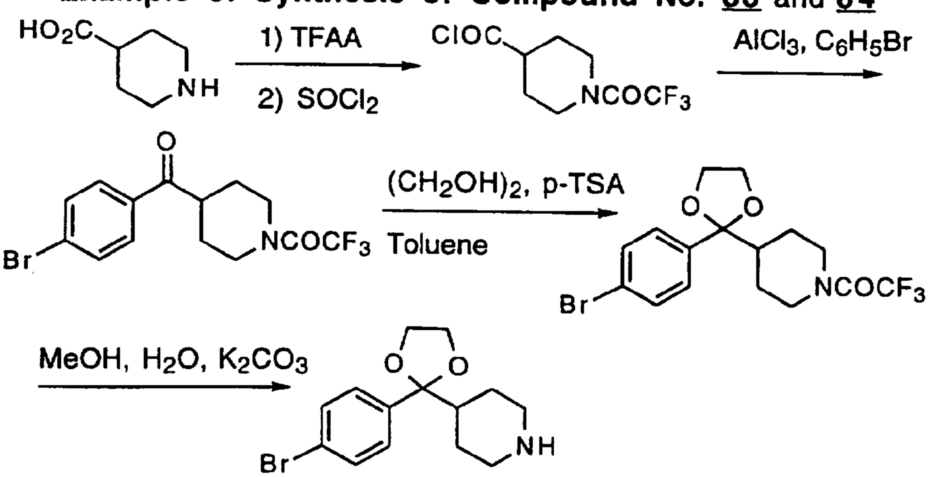
Example 7: Synthesis of Compound No. 25



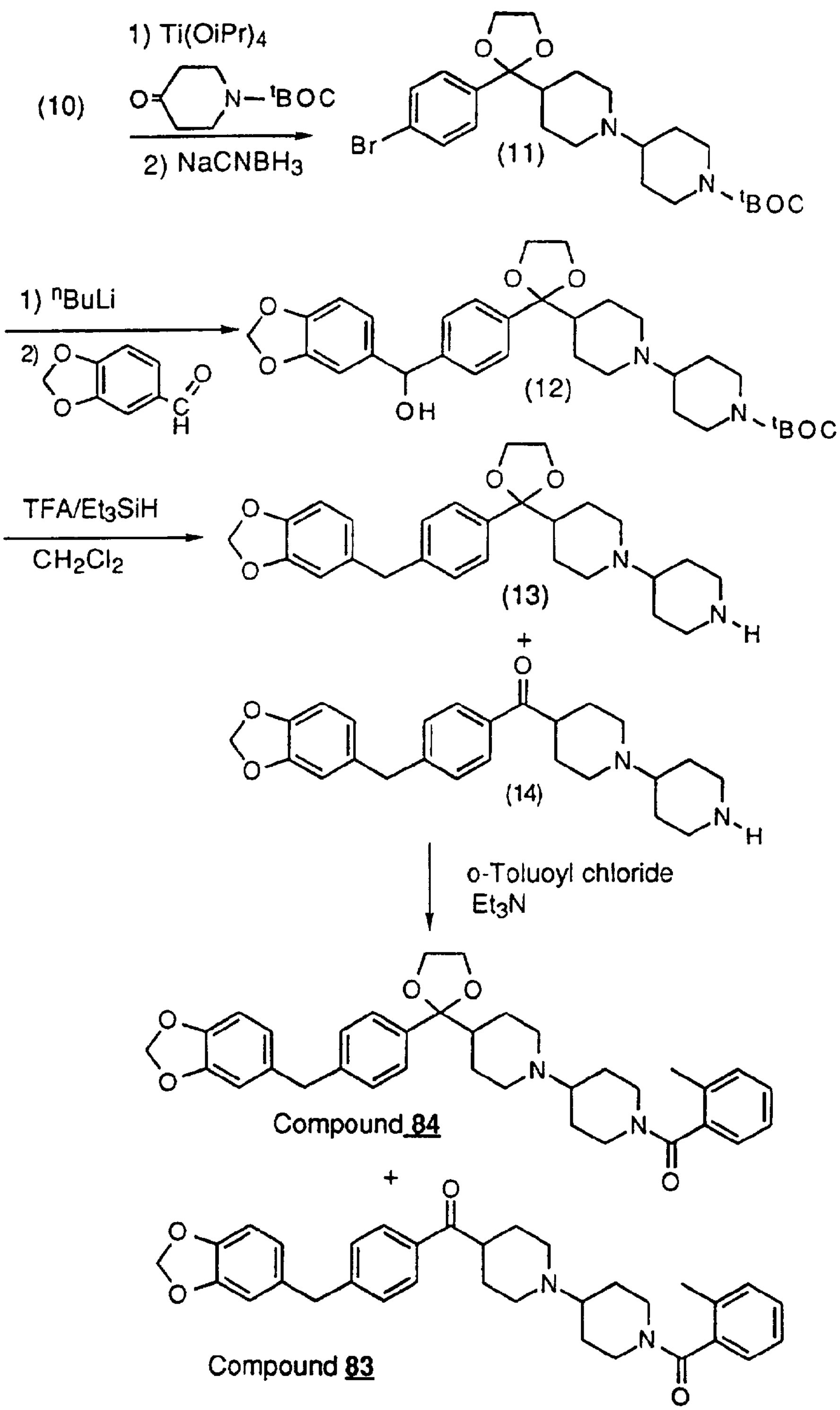
Compound **25**

Stir a solution of the product of example 6 (0.08 g) in DMF (1 ml) and add NaH (0.044 g), then after 10 min. add CH_3I and stir for 30 min. Work up in EtOAc-H_2O, dry, evaporate, purify by preparative tlc and convert to the HCl salt as in the foregoing preparation. Mp: 190-200°C, with decomposition; Mass spectrum: MH+ = 583.

Example 8: Synthesis of Compound No. 83 and 84



(10)



300 ml of trifluoroacetic anhydride (TFAA) was added to 96 g of isonipecotic acid at 0°C. After the addition, the reaction mixture was

heated at reflux for 4h. Excess TFAA was removed under vacuo and the reaction mixture taken up in EtOAc and washed with water and concentrated to give 160 g of the amide. 50 g of this amide was treated with 300 ml $SOCl_2$ and the reaction mixture heated at reflux overnight. At the end of this time excess $SOCl_2$ was removed under vacuo to give 54 g of the acid chloride.

11g $AlCl_3$ was added slowly to a solution of 10 g of the above acid chloride in 40 ml of bromobenzene at ambient temperature and the reaction mixture heated at reflux for 4 h. It was then cooled and poured into a mixture of conc. HCl and ice and product extracted with EtOAc. The organic layer was separated and washed with water, half saturated $NaHCO_3$ solution and concentrated to give 16.21 g of the ketone.

16.21 g of the ketone was dissolved in 200 ml toluene containing 25 ml ethylene glycol and 0.5 g p-toluenesulfonic acid. The reaction mixture was heated at reflux with azeotropic removal of water until no further water was collected. The reaction mixture was concentrated to give 17.4 g of the ketal.

17.4 g of the crude ketal was dissolved in 100 ml of CH_3OH and to this was added 25 ml of water and 12 g of K_2CO_3 and the reaction mixture stirred at ambient temperature overnight. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was separated and washed with water and brine and concentrated to give 12.55 g of (10).

A mixture of 6.5 g of (10), 4.15 g of N-BOC-4-piperidone and 10 ml of $Ti(OiPr)_4$ was stirred at ambient temperature overnight. The reaction mixture was cooled to 0°C and 3.2 g of $NaCNBH_3$ dissolved in 40 mL of CH_3OH was added. The reaction mixture was then allowed to warm to ambient temperature and stirred for 1 h., diluted with 100 ml of EtOAc and quenched with a mixture of 60 ml water/20 ml of conc. NH_4OH. The mixture was stirred for 1 h. and filtered though celite. The aqueous layer was extracted with 3x100 ml of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude was purified by flash chromatography using 100% EtOAc as eluent. To give 6.8 g, 66% of (11).

To a stirred solution of (11) in 25 mL of THF at -78°C was added 1.7 ml (1.6 M in Hex.) of ^{n}BuLi. The mixture was stirred at -78°C for 10 min., then 700 mg of piperonal dissolved in 5 ml of THF was added. The mixture was allowed to reach ambient temperature and stirred for 2 h. The mixture was quenched with 30 ml of water and extracted with 3x50 ml of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude was purified by silica gel flash chromatography using 10%Et_3N-ether to give 475 mg, 41.5% of (12).

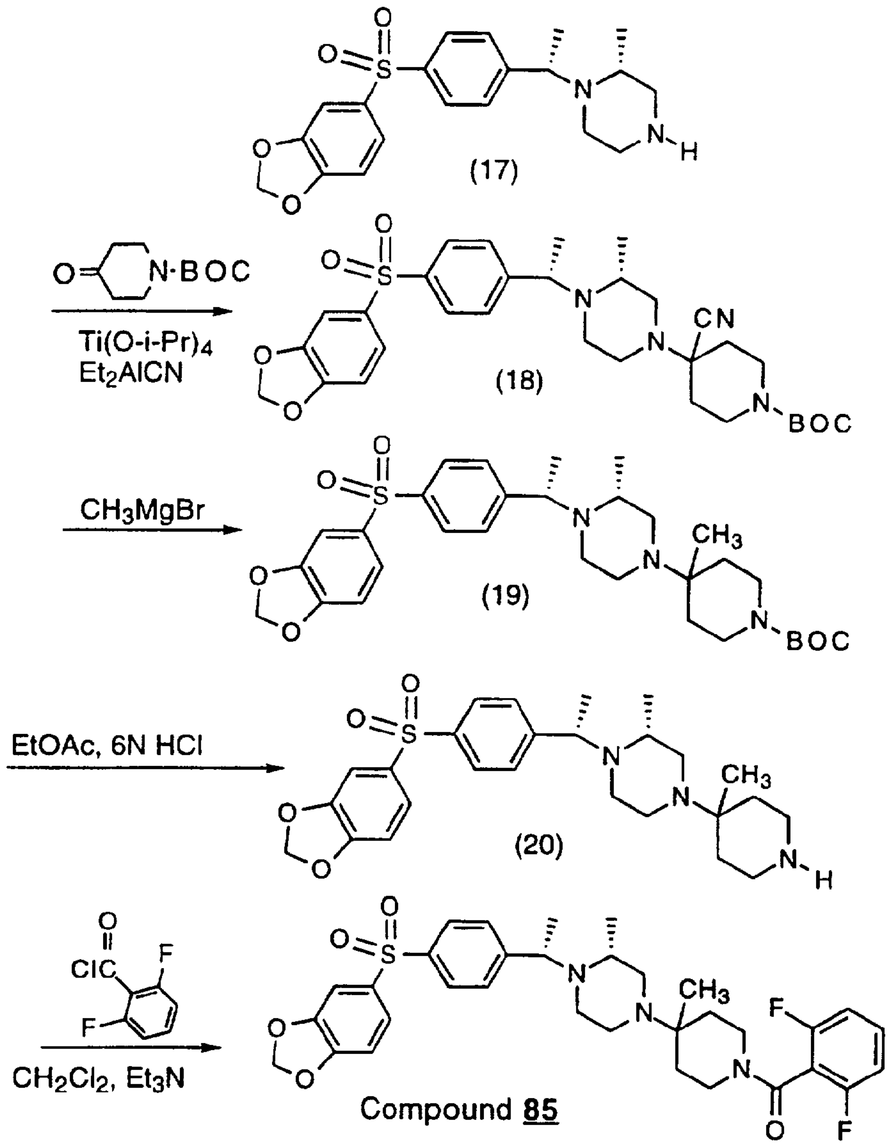
To a stirred solution of 475 mg of (12) and 1 ml of Et_3SiH in 10 ml of CH_2Cl_2 was added 3 ml of TFA. The mixture was stirred at ambient temperature for 2 h. The solvent was evaporated and the residue was taken up in 20 ml of CH_2Cl_2, washed with 20 ml of 10% NaOH. The aqueous layer was extracted with 3x30 ml of CH_2Cl_2, the combined organic layers were dried over $MgSO_4$, filtered and concentrated to give a mixture of (13) & (14) which was used without purification. (350 mg, 90%).

350 mg of the crude mixture of (13) and (14) and 1 ml of Et_3N in 10 ml of CH_2Cl_2 was treated with 0.5 ml (1.2 eq.) of o-toluoyl chloride for 3 h. The mixture was then concentrated and the residue purified by silica gel prep. TLC using 4% Et_3N-Et_2O to give compounds **83** and **84**. The HCl salts of compounds **83** and **84** were prepared by dissolving the free base in EtOAc and adding HCl-ether solution. After evaporating the solvent, the salts were collected as powder.

Compound No. **83** (50 mg, 54%) $(M+H)^+$ Cal: 525.2753; Found: 525.2746

Compound No. **84** (190 mg, 50%) $(M+H)^+$ Cal: 569.3015; Found: 569.3022

Example 9: Synthesis of Compound No. 85



The piperazine (17) (1.1 g, 2.8 mmol), prepared as described in example 1, is dissolved in CH_2Cl_2 (10 ml) followed by addition of the N-BOC piperidinone (0.85 g, 4.25 mmol) and $Ti(OiPr)_4$ (0.8 g, 2.8 mmol). The mixture is stirred overnight at room temperature. A 1 molar toluene solution of diethylaluminum cyanide (6.5 ml, 5.6 mmol) is added, via syringe, and the mixture stirred for an additional 20h. The mixture is then diluted with EtOAc and washed with 10% Na_2CO_3, water and brine. The organic phase is concentrated in vacuo and the residue

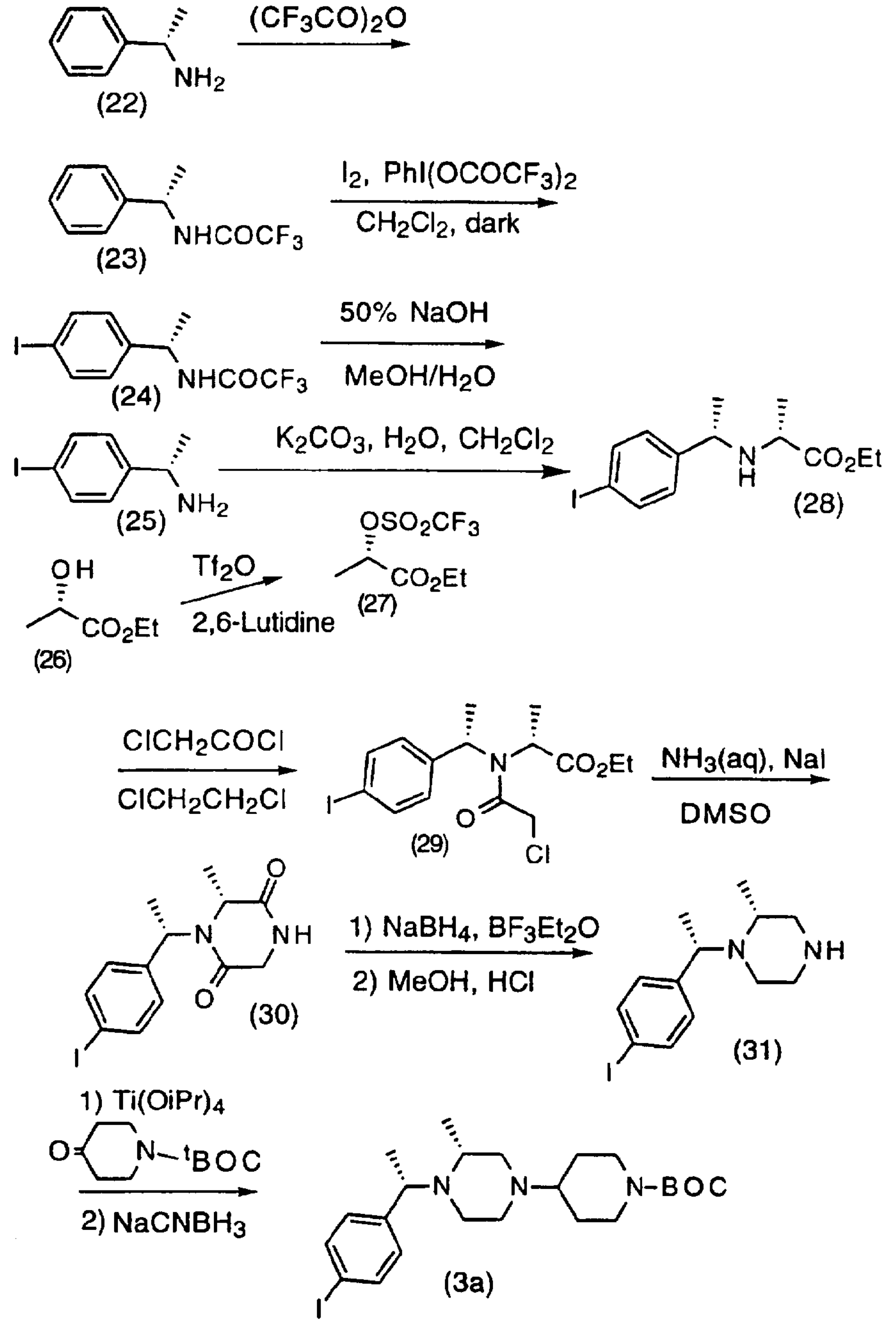
chromatographed through a silica gel column (1:1 EtOAc/hexane). The product (18) is collected as a colorless oil (0.93 g, 55%).

The cyano intermediate (18) (0.13 g, 0.19 mmol) is dissolved in THF (4 ml) followed by the addition of CH_3MgBr (0.64 ml, 3.0 M, 1.9 mmol), via syringe. After stirring for 10 min the temperature is raised to 60°C where stirring is continued for 2.5h. Cooling to room temperature is followed by quenching with water (1 ml) and then saturated $NaHCO_3$ (20 ml). After 10 min EtOAc (50 ml) is added, stirred vigorously, and separated. The organic layer is washed with brine and dried over Na_2SO_4. Filtration and concentration with under vacuum gives a viscous oil which is purified on silica gel prep TLC plates (100% EtOAc). The intermediate (19) is collected in 60% yield.

The N-BOC piperidine (19) (0.27 g, 0.4 mmol) is dissolved in EtOAc (10 ml) and 1.5 ml of a 6N HCl solution added with vigorous stirring. After 1.5h saturated $NaHCO_3$ is added until the pH was basic. CH_2Cl_2 (25 ml) is added and the layers separated, and the aqueous phase extracted with CH_2Cl_2. The organic layer is dried over Na_2SO_4, filtered and concentrated to collect 0.22 g, 95%, of (20) as a thick oil which solidifies under vacuum.

The amine (20) (0.025 g, 0.044 mmol) is dissolved in CH_2Cl_2 (1 ml) followed by the addition of Et_3N (11 ul, 0.08 mmol) and the 2,6-difluoro-benzoyl chloride (0.014 g, 0.08 mmol). After stirring at room temperature ovemight, saturated $NaHCO_3$ and CH_2Cl_2 are added. The layers are separated and the organic phase dried over Na_2SO_4. The solvent is removed and the residue dissolved in EtOAc. The solution was placed on a preparative TLC plate and eluted with EtOAc (100%). Compound <u>**85**</u> is collected as a clear oil (0.026 g), yield = 95%. This is converted to the dihydochloride salt as follows: The free amine (26 mg) is dissolved in 1 ml EtOAc and stirred while HCl / Et_2O is added until the pH persists at 2. The precipitate is transferred to a centrifuge tube and spun in a centrifuge. The supematant was removed and replaced with E_2O (gentle stirring with a spatula), and the sample spun again. The process is repeated 3X. After removal of the solvent, the solid is transferred to a vial where it is dried under vacuum. 15 mg of a white solid was collected (m.p. = 242-245 dec).

Example 10: Synthesis of Intermediate (3a) **from example 3**



Step 1

TFAA (150 ml, 1.06 mol) in CH_2Cl_2 (500 ml) was cooled to 0°C. A solution of (S)-α-methylbenzylamine (22) (100 g, 0.83 mol) in CH_2Cl_2 (200 ml) was added slowly over 30 min. The cooling bath was removed and the mixture was stirred for ~2h, transferred to a separatory funnel,

washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated to give 189 g (~100%) of (23) as a white solid

Step 2

Iodine (41 g, 162 mmol) was added to a solution of (23) (65.4 g, 301 mmol) in CH_2Cl_2 (500 ml) at room temperature. [Bis(trifluoroacetoxy)iodo]-benzene (75 g, 174 mmol) was added. The mixture was stirred for 30 min, a mild exotherm occurred (30°C), then kept in the dark overnight. The mixture was added slowly to a stirred mixture of $NaHCO_3$ (50 g), sodium bisulfite (10g) and water (600 ml), washing in with CH_2Cl_2. The mixture was stirred for 15 min, filtered and the filter cake was well washed with CH_2Cl_2 until TLC (100% CH_2Cl_2, Rf=0.75) shows no product in the washings. (Note: the initial solid contains considerable product which is moderately soluble in CH_2Cl_2). The filtrate was dried over anhydrous $MgSO_4$, filtered through a 1" pad of flash silica gel, washed with 2% Et_2O/ CH_2Cl_2. The filtrate was evaporated to a slurry, Et_2O (~75 ml) and hexanes (~700 ml) were added and the mixture was stirred for 30 min. The resulting solid was collected, washed well with hexanes, air dried and then dried under vacuum to give 63.05 g (61%) of (24) as a white solid. Filtrates were evaporated to an oil and some crystals, added hexanes (500 ml), stirred at room temperature for 1h, collected and additional 4.6 g (4%) of (24)

Step 3

(24) (10g, 29.15 mmol) was dissolved in CH_3OH (150 ml) and water (15 ml). 50% NaOH (30g) was added and the mixture was stirred at room temperature overnight (20 h). TLC (50% EtOAc/hex.) indicated consumption of starting material. Most of CH_3OH was removed in vacuo, the residue was dissolved in water and CH_2Cl_2, transferred to a separatory funnel and extracted with CH_2Cl_2. The extracts were combined, dried over anhydrous Na_2CO_3, filtered and concentrated to give 6.7 g (93%) of (25) as a white solid.

Step 4

Triflic anhydride (10.6 ml, 62.98 mmol) was added to a 0°C solution of (S) ethyl lactate (26) (7.0 ml, 61.75 mmol) in CH_2Cl_2 (100 ml) at 0°C. 2,6-Lutidine (7.55 ml, 64.83 ml) was added and the mixture was stirred for 1h. The mixture was transferred to a separatory funnel,

washed with 0.5 M HCl and brine, dried over anhydrous Na_2SO_4, concentrated almost to dryness, filtered through a plug of silica eluting with CH_2Cl_2, conc. to provide 10.8 g (70%) (27) as a reddish oil.

Step 5

(25) (6.7 g, 27.11 mmol) was added to a mixture of CH_2Cl_2 (90 ml), water (90 ml) and K_2CO_3 (5.5 g, 39.6 mmol). Ethyl (S) lactate triflate (27) (7.5 g, 29.82 mmol) was added and the mixture was stirred overnight (20 h). TLC (50% EtOAc/hex.) indicated consumption of starting material. Ammonia (conc.) (30 ml) was added, stirred 15 min, transferred to a separatory funnel, washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated to give 10.3 g (~110%) of (28).

Step 6

$ClCH_2OCl$ (12 ml, 150 mmol) was added to a solution of (28) (9.37g, 27.11) in dichloroethane (80 ml). The mixture was refluxed for 2h. TLC (20% EtOAc/hex.) indicated consumption of starting material. The solution was cooled to room temperature, diluted with CH_2Cl_2, water (200 ml) followed by K_2CO_3 (~15g) added in small portions. The mixture was stirred for an additional 15 min., transferred to a separatory funnel, washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated to give 11.53g (~110%) of (29).

Step 7

(29) (27.11 mmol) was dissolved in dimethyl sulfoxide (DMSO) (120 ml). Concentrated aqueous ammonia (24 ml) and NaI (13 g) were added. CH_3OH (10 ml) was used in the NaI. The mixture was stirred over the weekend (60h, overnight is sufficient). TLC (50% EtOAc/hex.) indicated consumption of starting material. Water (500 ml) was added, the mixture was stirred for 30 min and the resulting precipitate was collected via vacuum filtration. The precipitate was well washed with water and dried under vacuum to afford 8.2g (84%) of (30).

Step 8

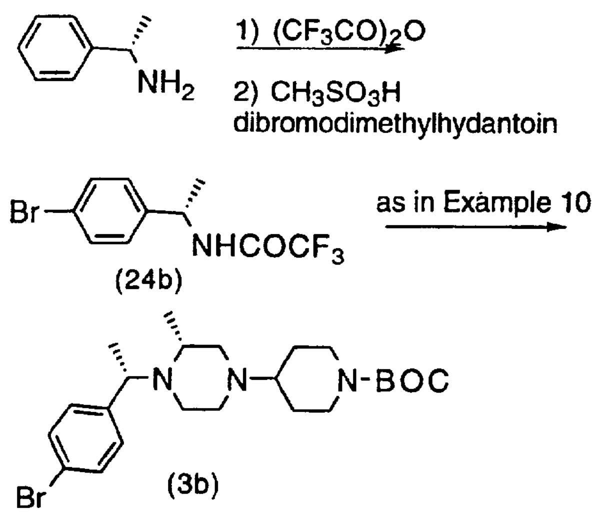
(30) (8.2 g, 22.9 mmol) was added to a mixture of $NaBH_4$ (8.66 g, 228.9 mmol) in dimethoxyethane (250 ml). Boron trifluoride etherate (16.9 ml, 137.3 mmol) was added and the resulting mixture was refluxed under nitrogen for 3h. TLC (5% CH_3OH/CH_2Cl_2) indicated consumption

of starting material. The mixture was cooled to 0°C, CH_3OH (60 ml) was added slowly and the resulting mixture was stirred for 20 min. Concentrated HCl (10 ml) was added slowly and the resulting mixture was refluxed for 1h. TLC (5% CH_3OH/CH_2Cl_2) indicated formation of a more polar product consistent with an amine. The mixture was cooled to room temperature and concentrated almost to dryness. The residue was partitioned between 2N NaOH and CH_2Cl_2, transferred to a separatory funnel and extracted with CH_2Cl_2. The extracts were combined, washed with water, dried over anhydrous Na_2SO_4 and concentrated to provide 6.5 g (87%) of (31) as an oil.

Step 9:

Intermediate (31) was converted to 3a using using procedures described in example 8.

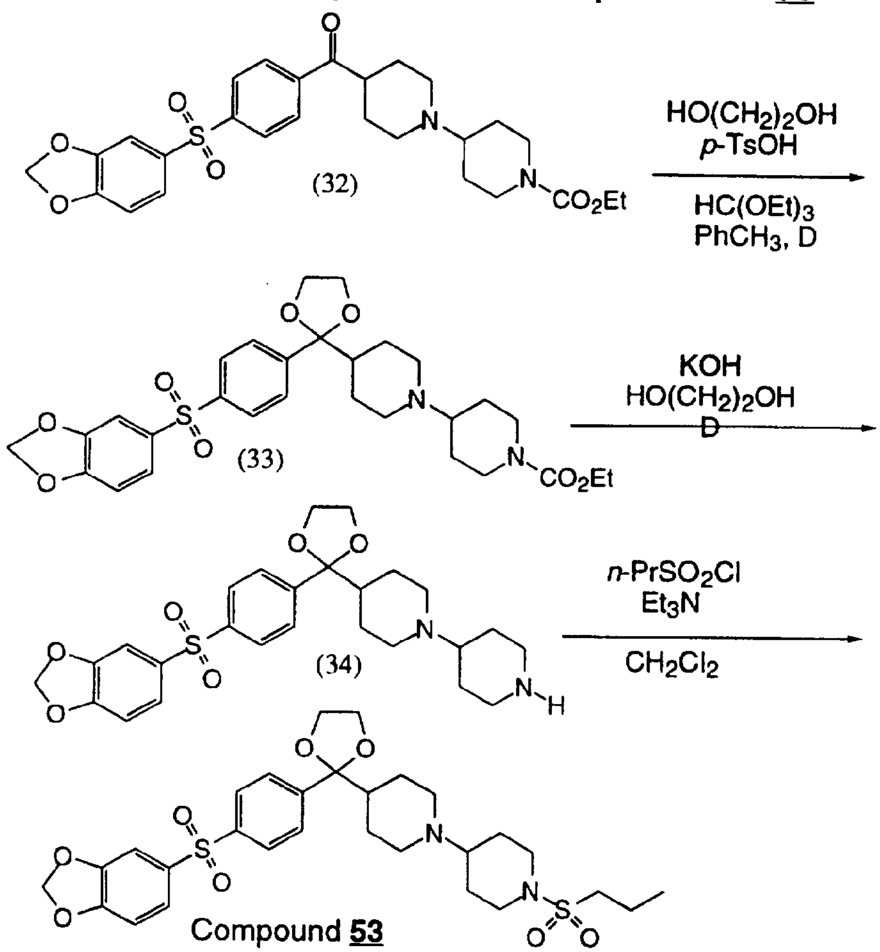
Example 11: Synthesis of Intermediate (3b) **from example 3**



A solution of TFAA (0.4 mol) in 300 ml cold CH_2Cl_2 is treated with 0.3 mol (S)-α-methylbenzylamine in 100 ml CH_2Cl_2. The resulting mixture is stirred with ice cooling for 30 minutes and at room temperature for 1.5 hours. The solution is again cooled in an ice bath and 80 ml CH_3SO_3H is added followed by 45 grams dibromodimethylhydantoin. Stirring is continued until the mixture is homogeneous, then the mixture is allowed to stand overnight in the dark. A solution of 20 g $NaHSO_3$ in 300 ml ice water is added. The organic layer is separated and washed twice with water and dried over $MgSO_4$. The solution is filtered through a 4" pad of flash-grade silica gel, eluting with 400 ml CH_2Cl_2, and

evalporated to a solid. The solid is suspended in 200 ml Et_2O and 1l hexane is added. After stirring 30 minutes, the solids are collected, washed with hexane, and dried to give 35.7 grams of intermediate (24b). This compound is converted to (3b) using the same sequence described in scheme 9.

Example 12: Synthesis of Compound No. 53



Compound 53

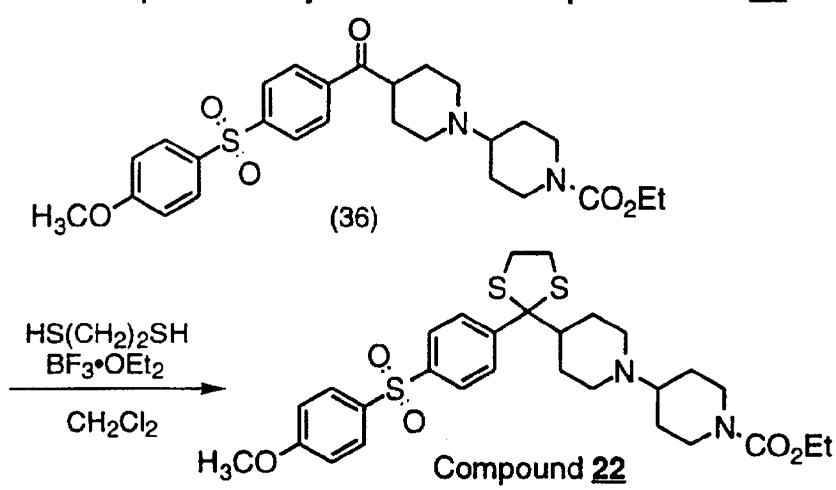
To a stirred solution of (32) prepared via the procedure described for intermediate (7) of example 14, but using N-ethyoxycarbonyl-4-piperidinone instead of N-tBOC-4-piperidinone (1.80 g, 3.41 mmol) in toluene (34 ml) was added dry ethylene glycol (1.33 ml, 23.8 mmol), triethylorthoformate (1.70 ml, 10.2 mmol) and *p*-toluenesulfonic acid monohydrate (0.97 g, 5.12 mmol). The reaction was heated overnight at 55°C under nitrogen. The mixture was diluted with CH_2Cl_2, washed sequentially with 1N NaOH and brine, dried over Na_2SO_4, filtered and

concentrated in vacuo. The resulting product (33) (2.40 g) was used without further purification.

The crude ketal (33) (0.83 g, ~1.45 mmol) was dissolved in ethylene glycol (44 ml) and crushed KOH (2.90 g, 51.6 mmol) was added to the rigorously stirred solution. The reaction was heated for 24 h at 100°C. After cooling to room temperature, the mixture was diluted with EtOAc followed by the addition of 1N NaOH. The aqueous portion was extracted with EtOAc and the combined organics washed several times with 1N NaOH. The crude solution was dried over Na_2SO_4, filtered, and concentrated to yield 0.31 g of (34) which was used without further purification.

To a solution of (34) (31.4 mg, 62.8 μmol) in CH_2Cl_2 (0.60 ml) was added *n*-propylsulfonyl chloride (20 μL, 178 μmol) and Et_3N (30 μL, 215 μmol). The reaction was stirred for 2 h at room temperature under nitrogen. The mixture was concentrated under reduced pressure and purified by PTLC (10/90 CH_3OH/CH_2Cl_2), yielding (35) (12.3 mg, 32% over 3 steps). LRMS (FAB): (M+H)=606

Example 13: Synthesis of Compound No. 22



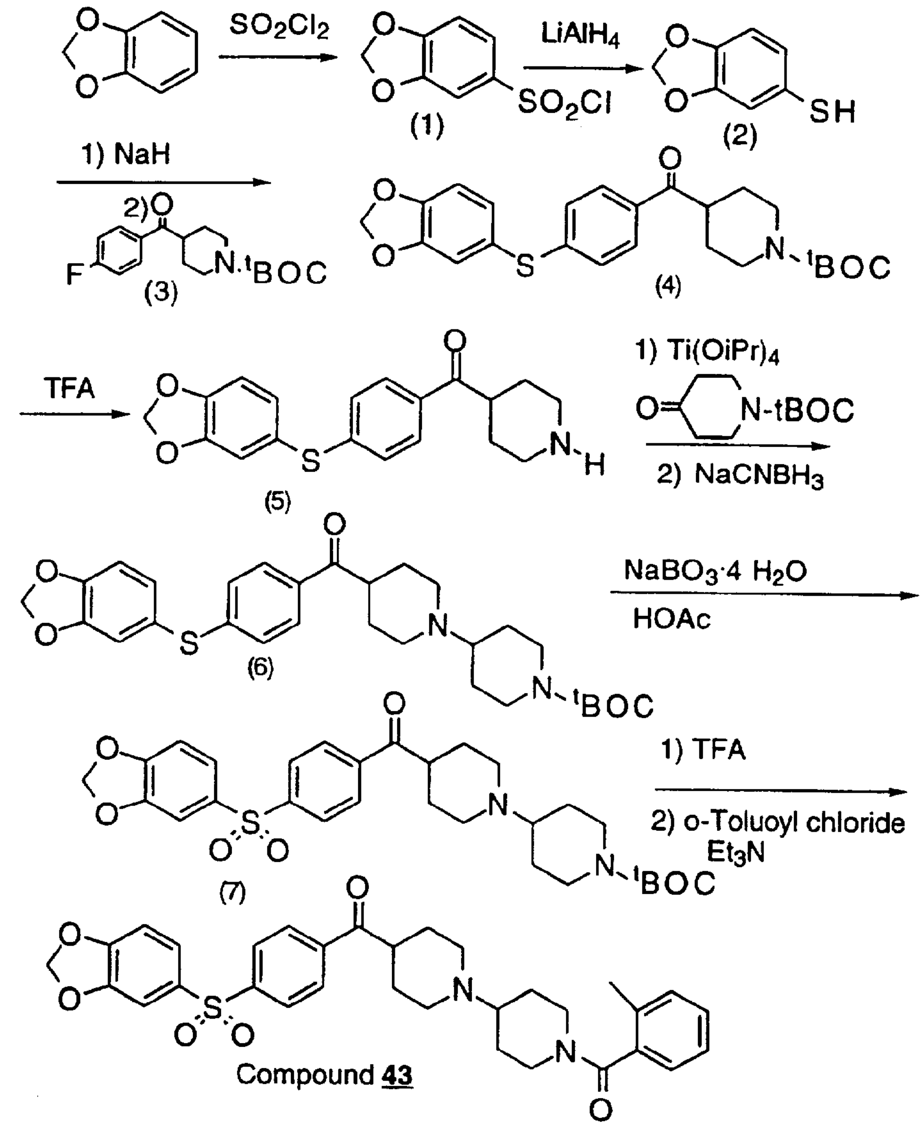
(36)

Compound 22

To a solution of (36) prepared via the procedure described for intermediate (7) of example 14, substituting 4-mercaptoanisole for 4-mercaptomethylenedioxybenzene and N-ethyoxycarbonyl-4-piperidinone for N-tBOC-4-piperidinone (29.5 mg, 58.9 μmol) in CH_2Cl_2 (0.24 ml) was added ethanedithiol (7.4 μL, 88 μmol) and BF_3•OEt_2 (11 μL, 88 μmol). The reaction was stirred overnight at room temperature under nitrogen, then diluted with CH_2Cl_2 and washed with 10% NaOH.

The crude mixture was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by PTLC (10/90 CH_3OH/CH_2Cl_2) yielded **37** (17 mg, 50% yield). LRMS (FAB): (M+H)=591.

Example 14: Synthesis of Compound 43



Compound 43

To a stirred solution of 41 ml of anhydrous DMF was added 43 ml of SO_2Cl_2 at 0-10°C followed by slow addition of 61 grams of methylenedioxy-benzene. After the addition was completed, the mixture was heated at 80°C for 10 min., and then 5-10 min. at 110°C. The reaction mixture turned to dark brown. The mixture was cooled to 40°C and was poured into a mixture composed of 200 ml H_2O/200g crushed ice/300 ml $CHCl_3$. Two layers were separated, the organic layer was

dried over $MgSO_4$, filtered, and concentrated to give a crude product (1) which was triturated with 100 ml of hexanes. (60.6 g, 53%)

To a stirred suspension of 16 g LAH in 500 ml of THF at 0°C, was added dropwise 60.6 g of (1) dissolved in 100 ml of THF. The temperature was allowed to reach RT and the mixture was stirred at this temperature for 2 h.. The reaction mixture was then quenched carefully with 1N HCl at 0°C to pH=1, diluted with 1 L EtOAc. The organic phase was washed with 500 ml of water, dried over $MgSO_4$, filtered and concentrated to give a crude which was used directly in the next step without purification. (29 g, 68%)

28 g of the crude thiol (2) dissolved in 20 ml of DMF was added to a stirred suspension of 8 g of NaH(60%) in 80 ml of DMF. The mixture was stirred at RT for 1 h., ketone (3) dissolved in 150 ml of DMF was added at once. The mixture was heated at 70°C over night. The mixture was diluted with 400 ml of CH_2Cl_2 and then quenched with 300 ml of water. The organic phase was washed with 3x200 ml of water, dried with $MgSO_4$, filtered and concentrated to give crude (4) which was purified by flash chromatography using EtOAc/Hex./CH_2Cl_2=1/4.5/4.5 as eluents. (35 g, 53%)

To a stirred solution of 6 g of (4) in in 100 ml of CH_2Cl_2 was added 10 ml of TFA. The mixture was stirred at RT for 1 h. The solvent was eliminated under reduced pressure and the residue was taken up in 100 ml of CH_2Cl_2 and extracted with 3x60 ml of CH_2Cl_2. The combined organic phase was chloride, quenched with 50 ml of 10% NaOH. The aqueous phase was dried over $MgSO_4$, filtered and concentrated to give crude (5), used without purification. (4.6 g, 100%)

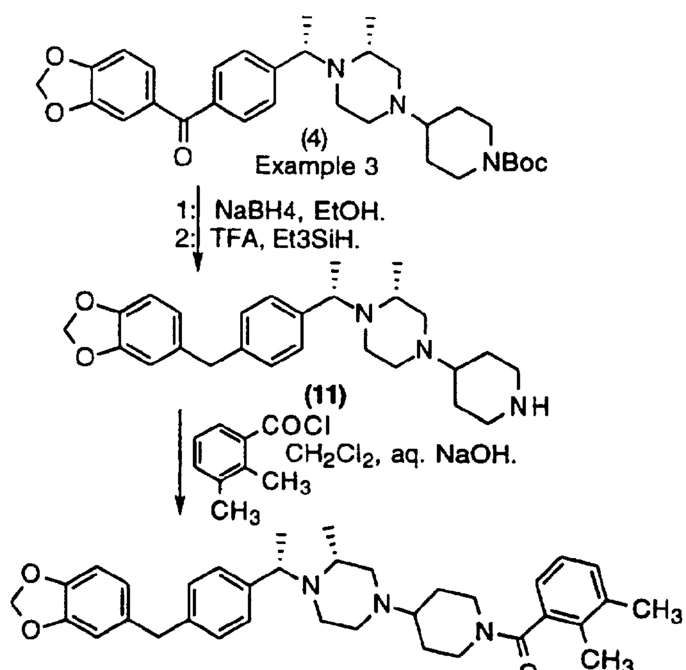
A mixture of 3.4 g of (5) 2.4 g of N-BOC-4-piperidone and 5.9 ml of $Ti(OiPr)_4$ was stirred at RT over night. 1.6 g of $NaCNBH_3$ dissolved in 40 ml of CH_3OH was added at 0°C. The mixture was stirred at RT for 1 h. diluted with 100 ml of EtOAc, quenched with a mixture of 60 ml water/20 ml of NH_4OH. The mixture was stirred at RT for 1 h. and filtered though celite. The aqueous phase was extracted with 3x100 ml of EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude (6) was purified by flash chromatography using 100% EtOAc as eluent. (3.8 g, 73%)

To a solution of 1.32 g of (6) in 15 ml of HOAc was added 1.41 g of $NaBO_3 \cdot 4H_2O$, and the mixture was stirred at RT for 3 days. The solvent was evaporated and the residue was quenched with 20 ml of 10% NaOH, then extracted with 3x50 ml of EtOAc. The combined organic extract was dried over $MgSO_4$, filtered and concentrated. The crude (7) was purified by silica gel prep TLC using 20%EtOH-EtOAc. (620 mg, 44%)

620 mg of (7) in 15 ml of CH_2Cl_2 and 5 ml of TFA was stirred at RT for 3 h. The solvent was evaporated and residue was treated with 10% NaOH, then extracted with EtOAc. The organic extract was dried over $MgSO_4$, filtered and concentrated to give crude product (510 mg, 100%). 0.052 mmol of the resultant crude free amine was reacted with 1.2 eq. of o-toluoyl chloride and 1.3 eq. of Et_3N in 3 ml of CH_2Cl_2 for 3 h. The mixture was concentrated and the residue was purified by silica gel preparative TLC using 20% EtOH-EtOAc. (18 mg, 50%) $(M+H)^+$ Cald: 575.2216; Found: 575.2223.

The HCl salts were prepared by dissolving <u>43</u> in EtOAc and adding HCl-ether solution. After evaporating the solvent, the salts were collected as powder.

Example 15: Preparation of Compound No. <u>82</u>

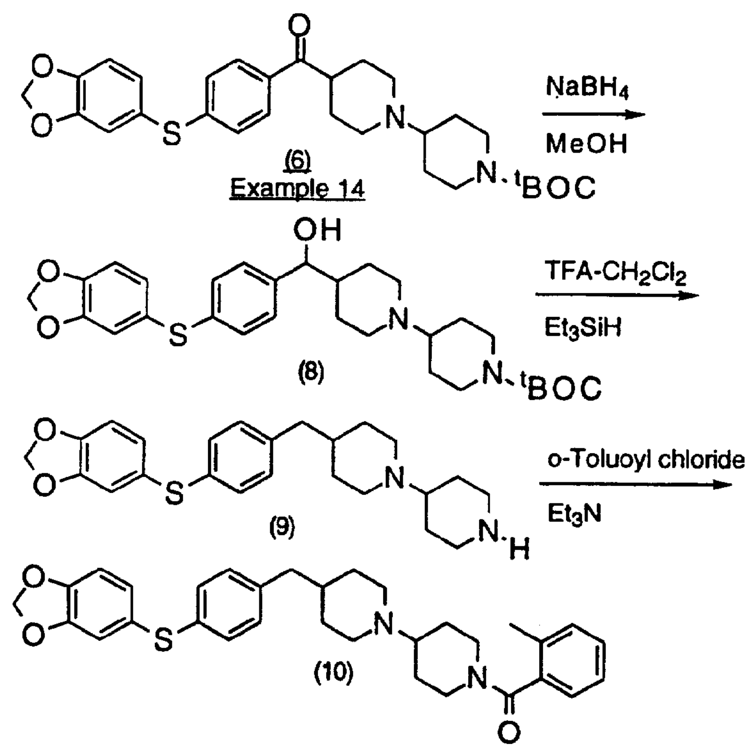


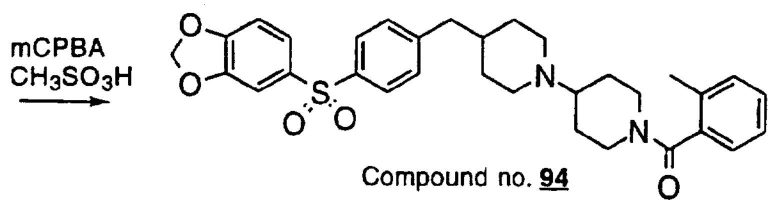
Compound no. <u>82</u>

Stir a solution of compound (**4**) from Example 3 (0.5 g) and $NaBH_4$ (0.2 g) in ethanol (3 ml) at RT for 3 h. Add water, extract with CH_2Cl_2, dry over $MgSO_4$ and evaporate. To the residue in CH_2Cl_2 (5 ml) add triethylsilane (3 ml) and TFA (3 ml), relux for 3 h., evaporate, partition with CH_2Cl_2 and 1N aq. NaOH, dry and evaporate to obtain (11) as a thick oil, used as such in subsequent acylation experiments.

Stir a mixture of (11) (0.03 g), CH_2Cl_2 (2 ml) and 1N aq. NaOH (2 ml) and add 2,3-dimethylbenzoyl chloride (0.07 g). Stir at RT for 18 h., extract with CH_2Cl_2, dry and evaporate. Dissolve the residue in 1:1 CH_2Cl_2:acetone and filter through a small plug of silica gel, washing with the same solvent mixture. Evaporate, dissolve the residue in a small volume of CH_2Cl_2 and precipitate the dihydrochloride by adding to excess HCl in Et_2O as described in earlier preparations Wash with Et_2O and dry to obtain the product compound No. 82 as an off-white powder (0.036 g). Mp: 207-212°C, with decomposition; MS: MH+ = 554.

Example 16: Preparation of Compound No. 94



(10) 

Compound no. **94**

To a stirred solution of 899 mg (1.72 mmol) of (4), prepared as described in Example 14, in 15 ml of anhydrous CH_3OH is added by portion 130 mg of $NaBH_4$. The mixture is stirred at room temperature for 30 min. and then quenched with 15 ml of 10% NaOH solution. The aqueous layer is extracted with 4x20 ml of EtOAc. The combined organic layers are dried over Na_2SO_4, filtered and concentrated to give 859 mg (95%) of (8).

To a stirred solution of 850 mg of crude (8) in 5 ml of CH_2Cl_2 is added 563 mg (3 eq.) of triethylsilane, followed by 2 ml of TFA. The mixture is stirred at room temperature for 3 hrs. and then is concentrated. The residue is taken up in 15 ml of CH_2Cl_2 and 15 ml of 10% NaOH. The aqueous layer is extracted with 3x15 ml of CH_2Cl_2. The combined organic layers are dried over $MgSO_4$, filtered and concentrated to give 600 mg (92%) of crude (9).

To a stirred solution of 600 mg of (9) and 455 mg of Et_3N in 5 ml of CH_2Cl_2 is added 464 mg of o-toluoyl chloride. The mixture is stirred at room temperature for 2 hrs. The mixture is quenched with 20 ml of water, extracted with 3x20 ml of EtOAc. The combined organic layers are dried over $MgSO_4$, filtered and concentrated to give a crude. Purification on silica gel prep TLC affords 555 mg (70%) of (10).

To a stirred solution of 43 mg of (10) and 0.5 ml of CH_3SO_3H (0.5 M CH_2Cl_2) in 5 ml of CH_2Cl_2 is added at 0°C, 58 mg (57-86%) of mCPBA. The mixture is stirred at 0°C for 1 h. and is quenched with 15 ml of 10% $NaHCO_3$. The aqueous layer was extracted with 3x15 ml of EtOAc. The combined organic layers are dried over $MgSO_4$, filtered and concentrated to give a crude product. Purification on silica gel prep. TLC affords 36 mg (80%) of free base of compound number **94**. The HCl salt is prepared by dissolving the free base in EtOAc and adding HCl-ether solution. After evaporating the solvent, the salts are collected as powder. $(M+H)^+$ Cal: 561.2423; Found: 561.2416.

Using appropriate starting materials in the above procedures, with modifications well known in the art, the compounds exemplified in the following table are prepared:

TABLE OF COMPOUNDS

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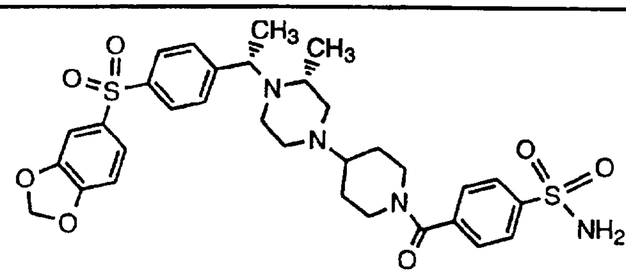
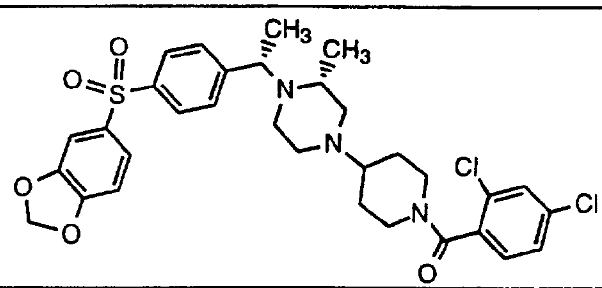
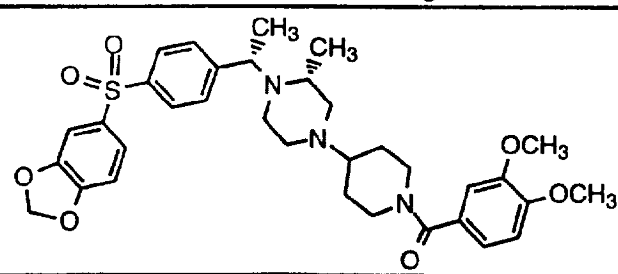
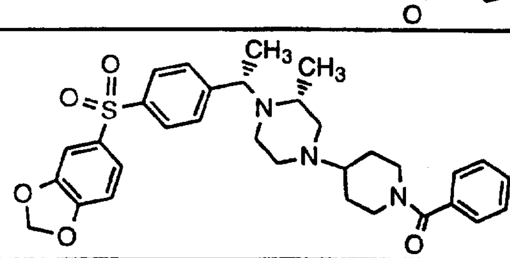
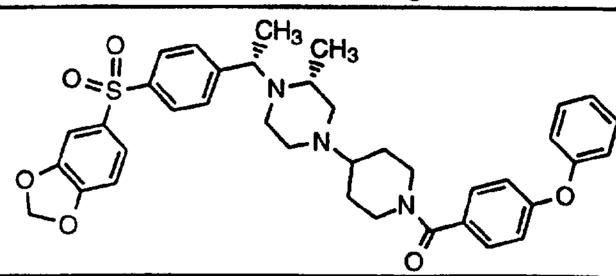
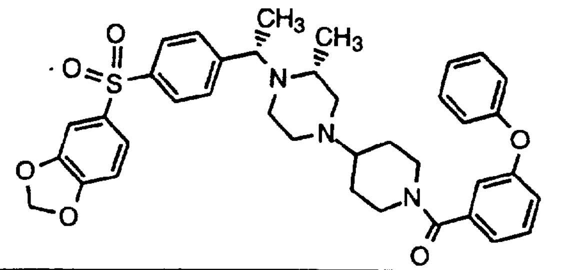
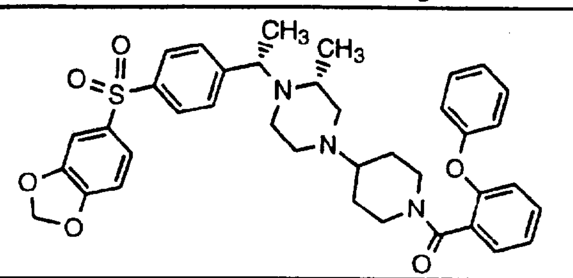
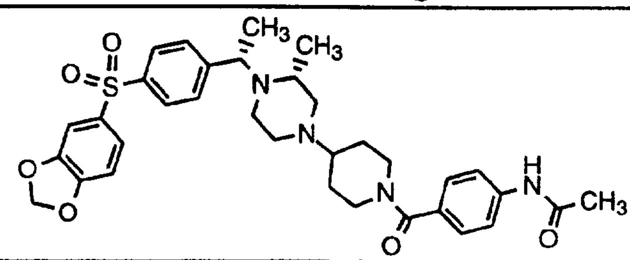
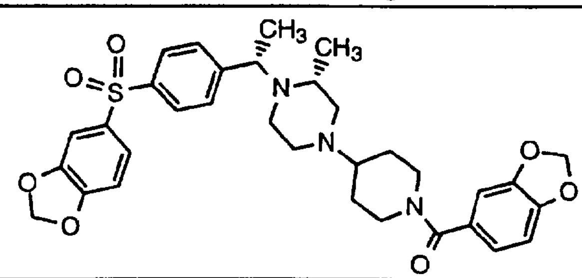
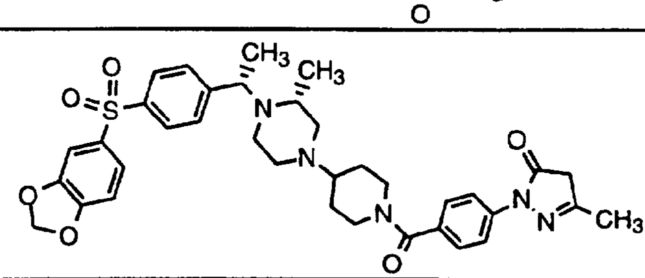
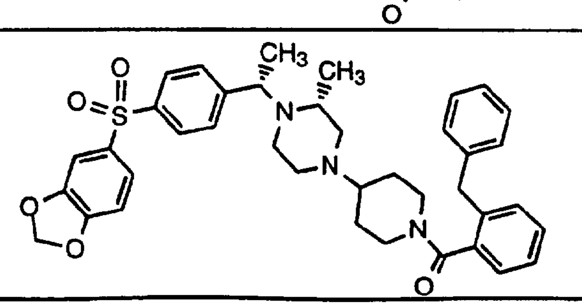
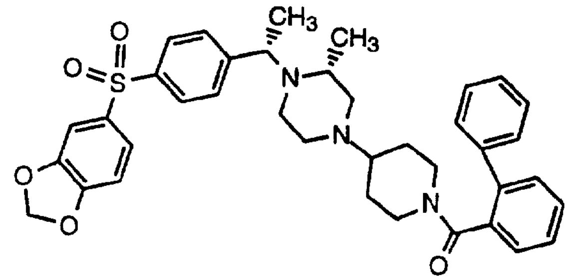
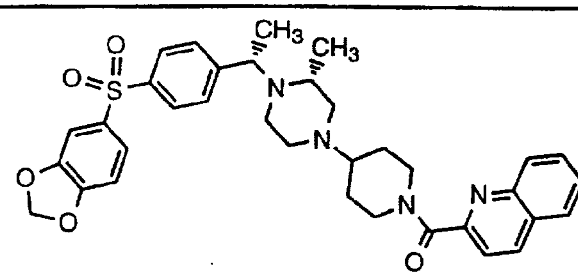
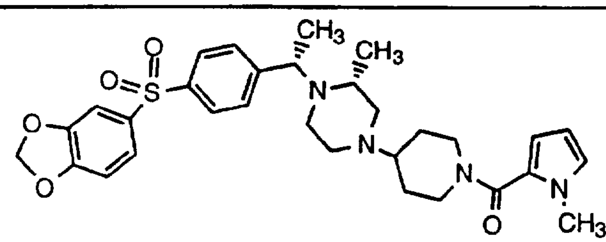
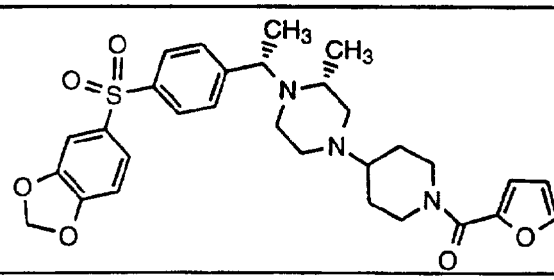
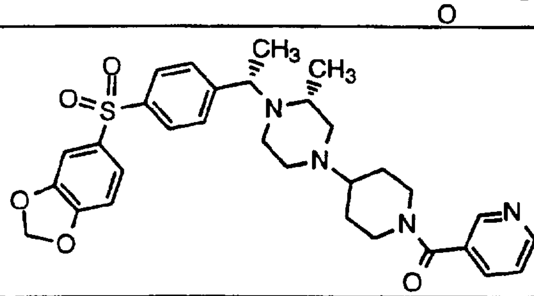
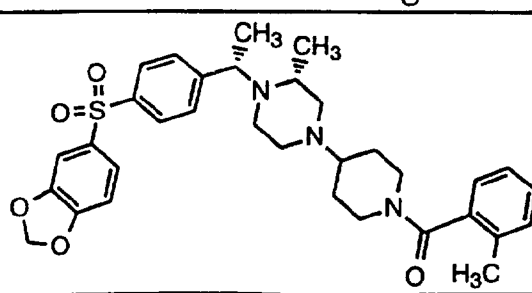
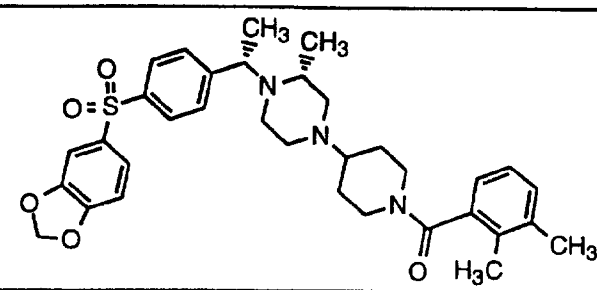
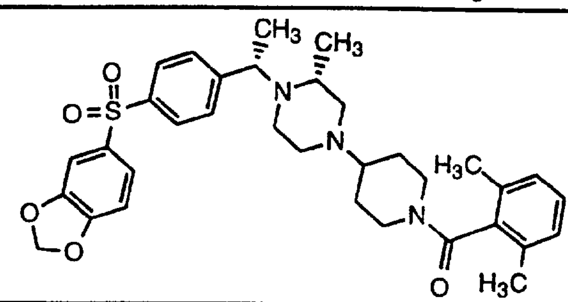
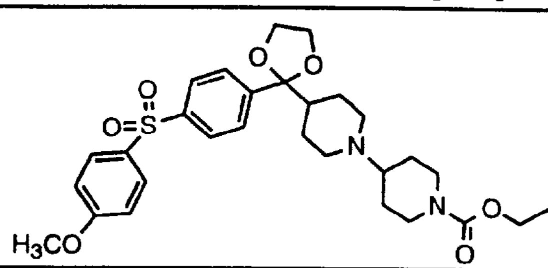
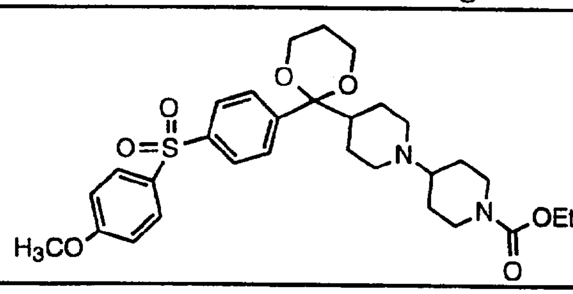
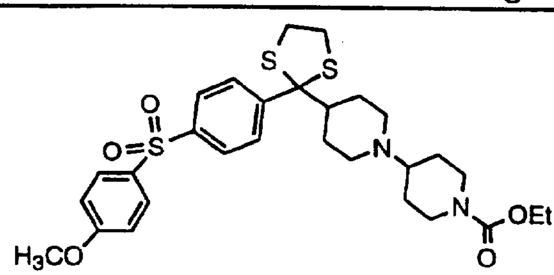
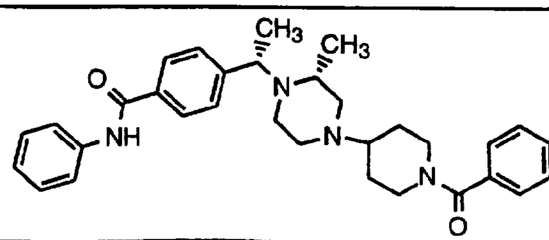
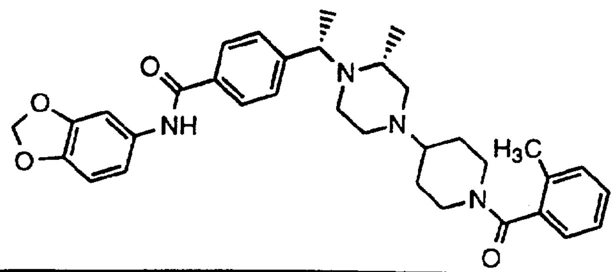
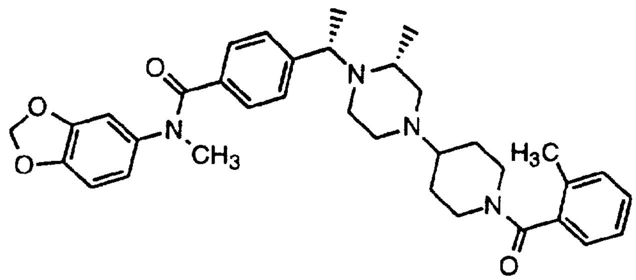
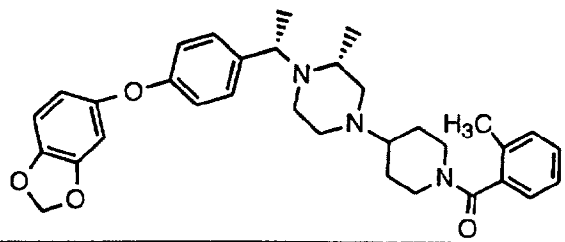
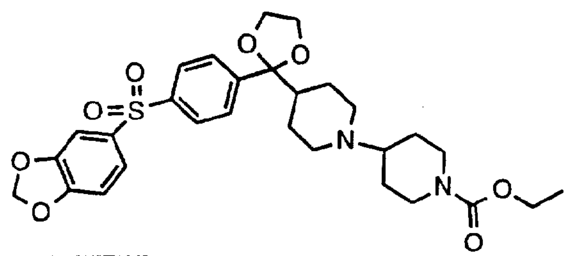
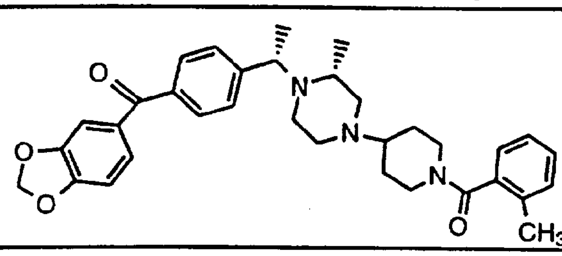
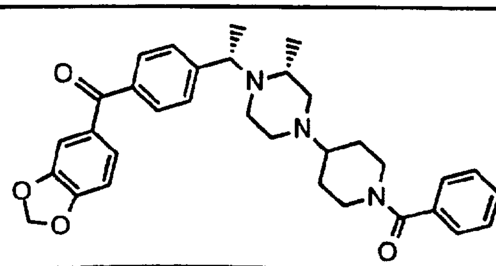
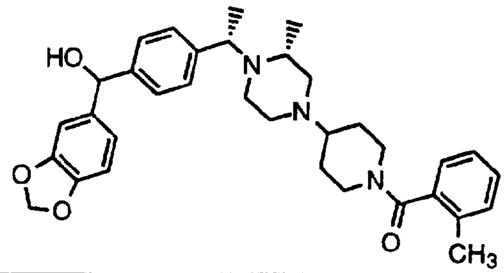
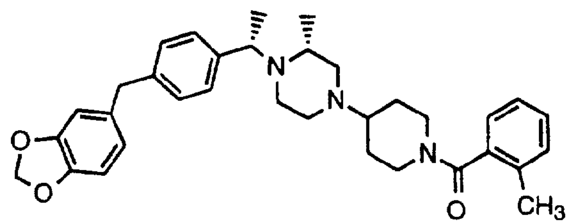
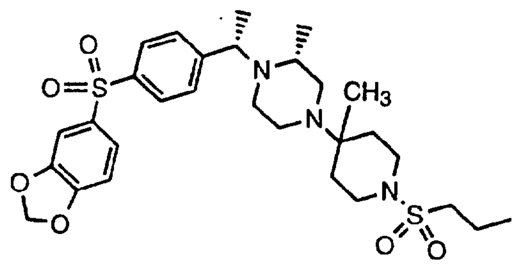
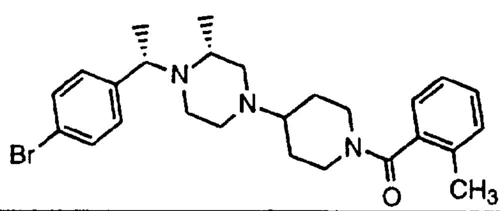
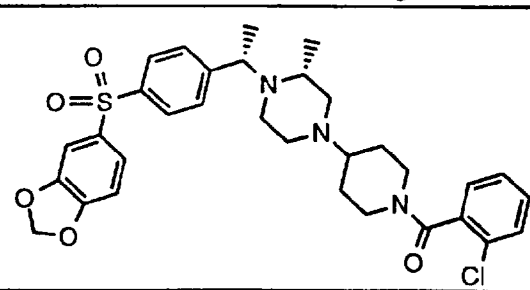
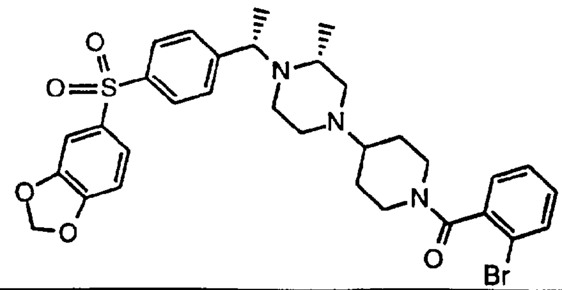
1		-
2		-
3		-
4		mp=215-225°C (dec) MS MH+=574
5		-

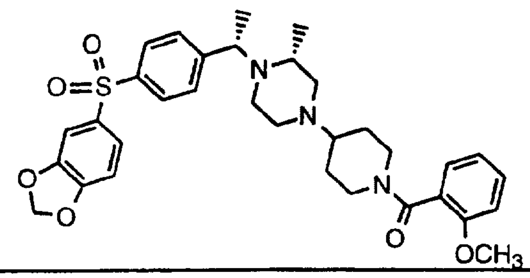
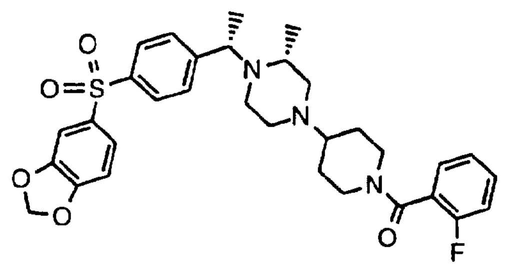
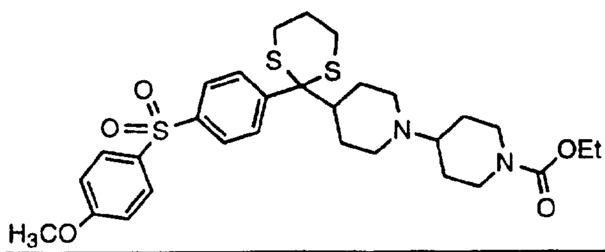
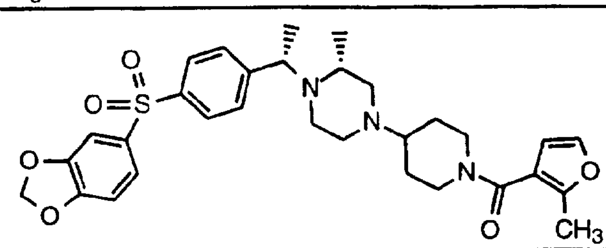
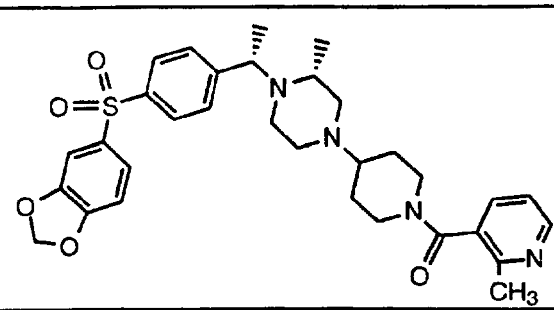
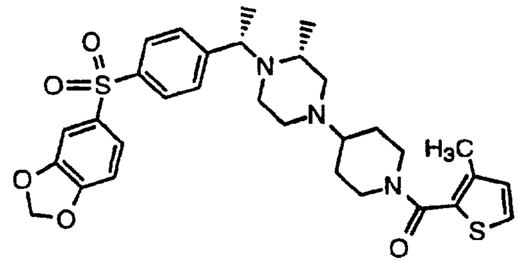
6		–
7		–
8		–
9		–
10		–
11		–

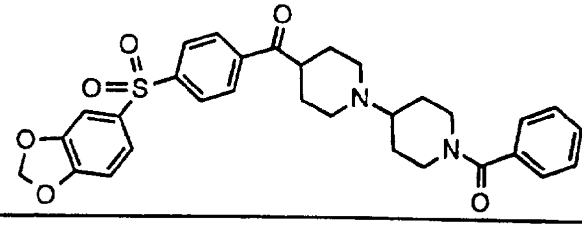
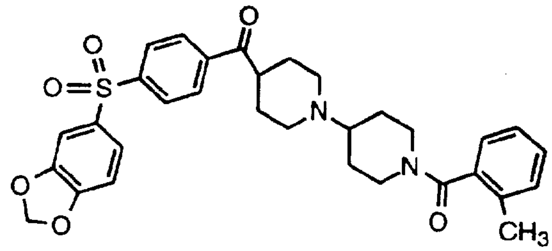
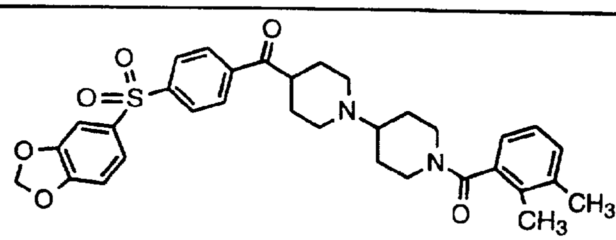
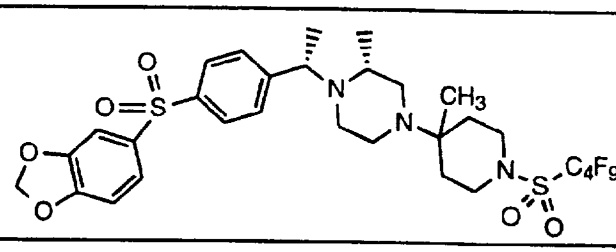
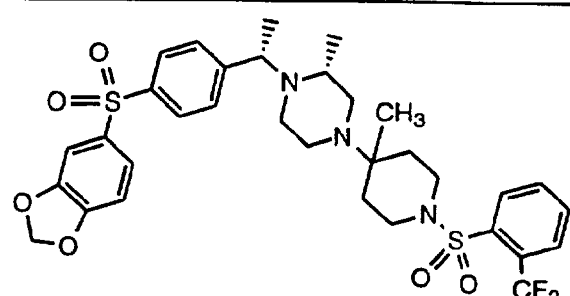
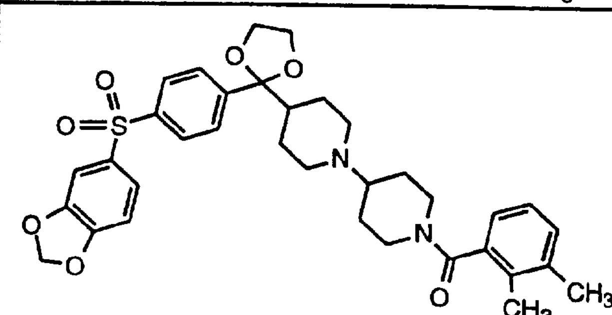
12		–
13		–
14		–
15		–
16		–
17		mp=182-190 oC (dec) MS MH+=588

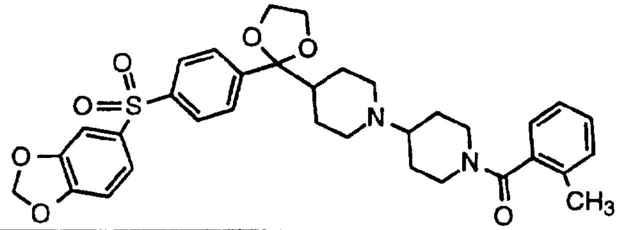
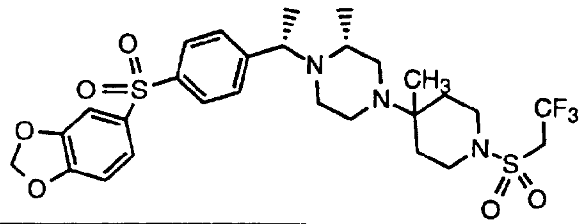
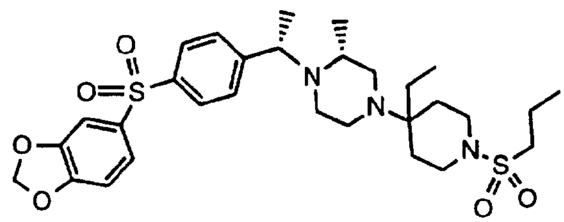
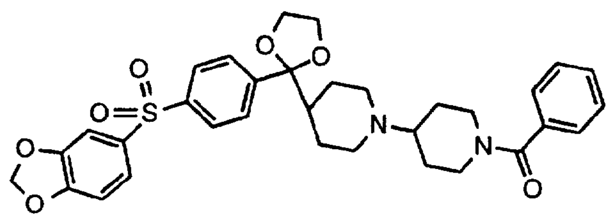
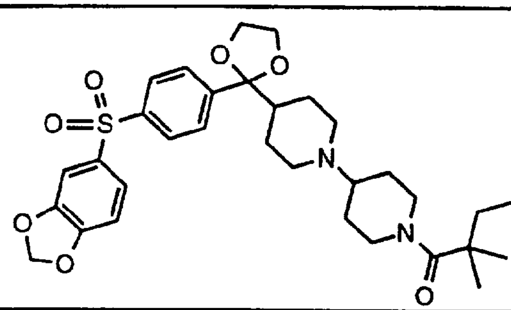
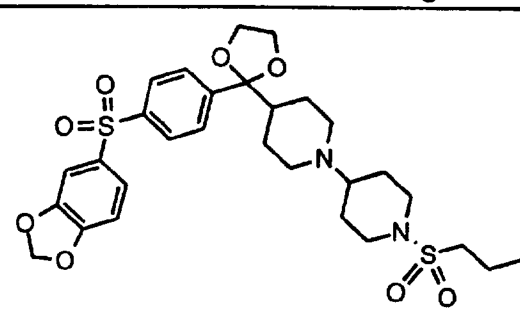
18		–
19		–
20		–
21		–
22		LRMS (FAB) Calc. for $C_{29}H_{38}O_5N_2S_3$ (M+H): 591 Found: 591
23		–

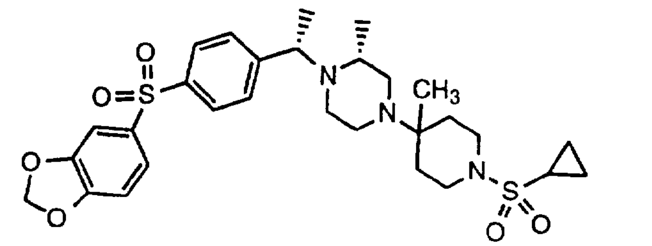
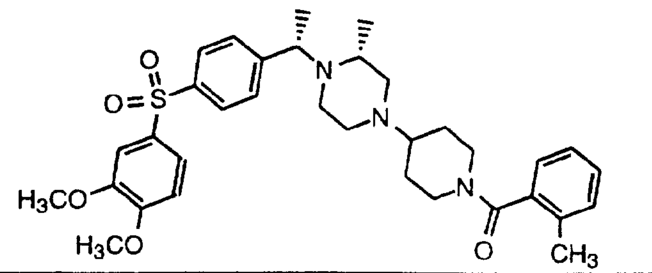
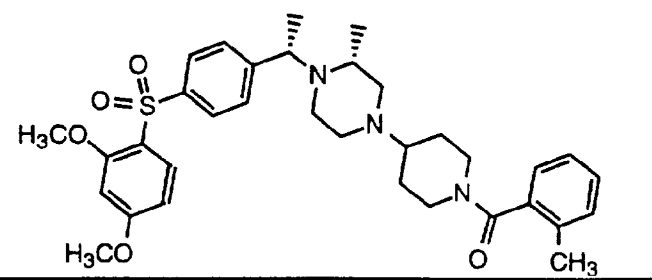
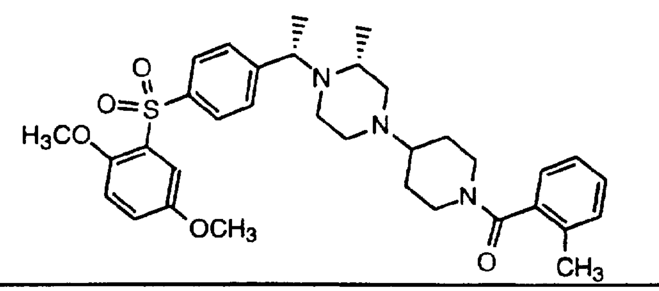
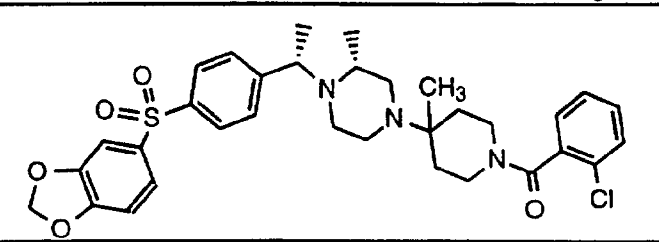
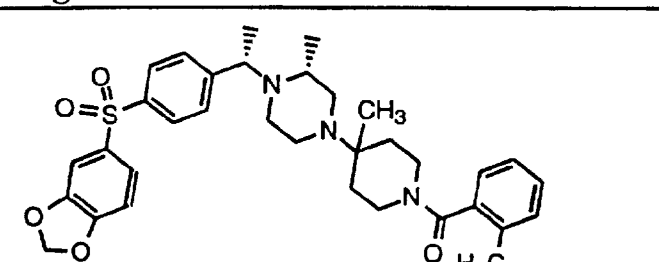
24		mp=220-230°C (dec) MS MH+=569
25		mp=190-200°C (dec) MS MH+ = 583
26		-
27		HRMS Calcd: 573.2278 Found: 573.2271
28		mp = 200-210°C (dec) MS MH+ = 554
29		-

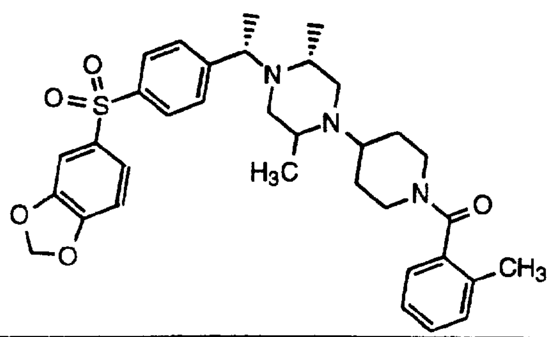
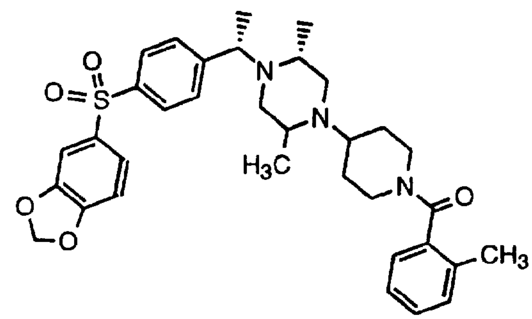
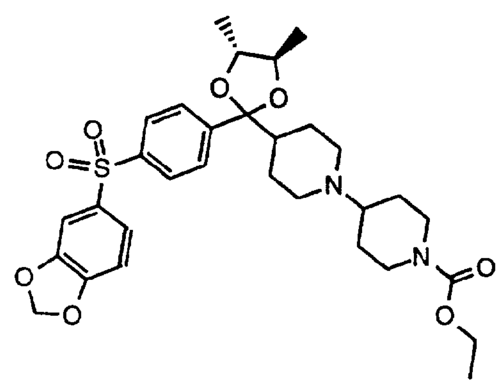
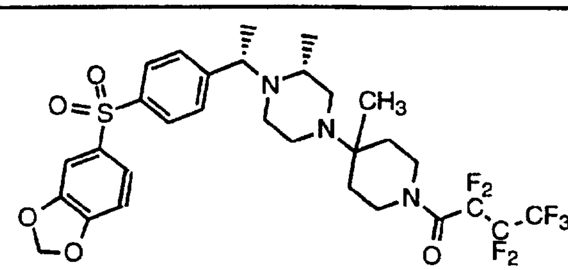
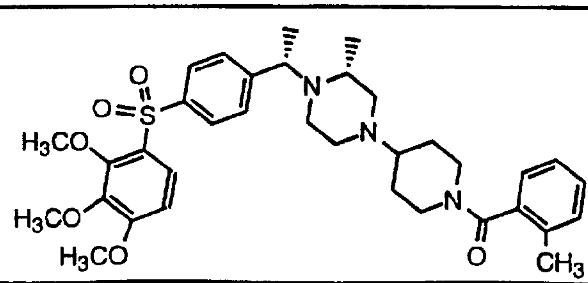
30		mp = 85-95°C (dec) MS MH+ = 556
31		mp= 210-215°C (dec) MS MH+=540
32		mp=235-237°C (dec)
33		–
34		mp=185-200°C (dec) MH+ 608/610
35		mp=178-190°C (dec) MS MH+ = 652/654

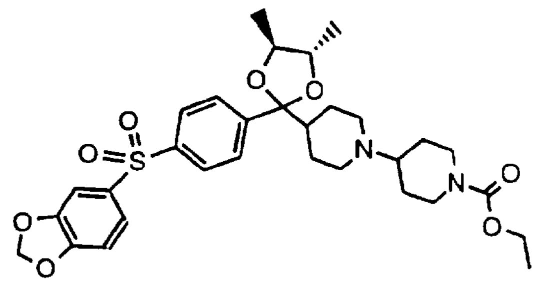
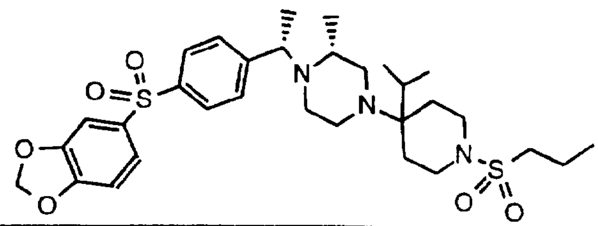
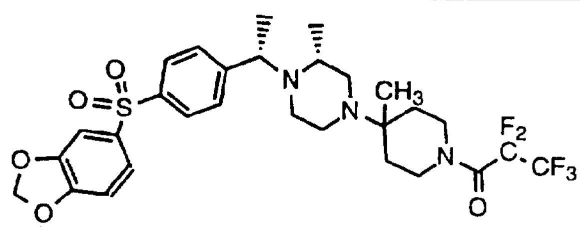
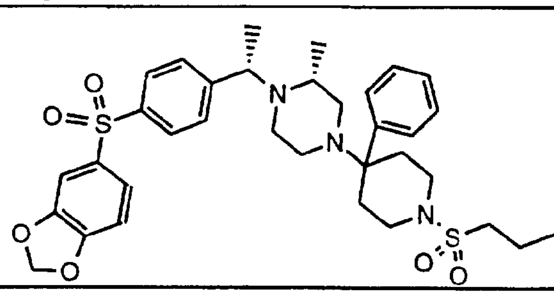
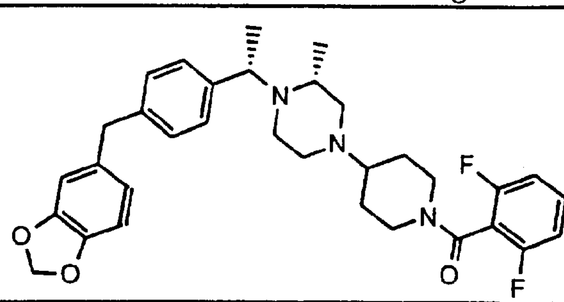
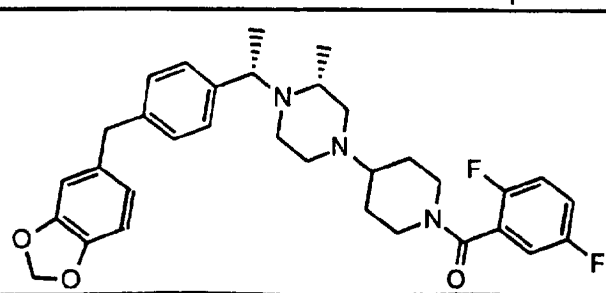
36		mp=180-190°C (dec) MH+= 604
37		mp=180-195°C (dec) MH+=593
38		–
39		mp= 190-205°C (dec) MS MH+=578
40		–
41		mp = 180-290°C (dec) MS MH+=594

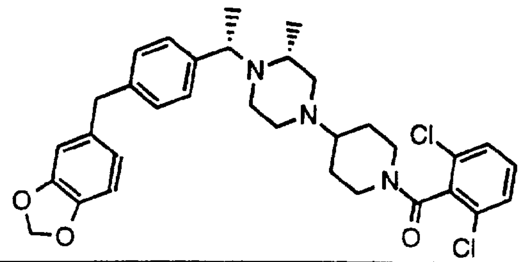
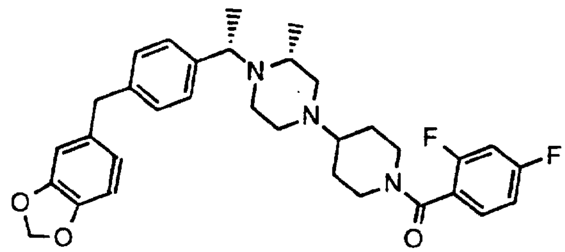
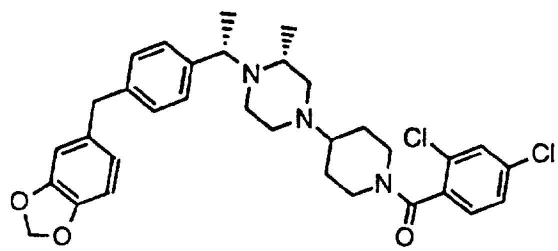
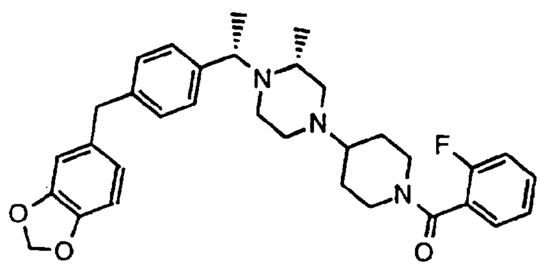
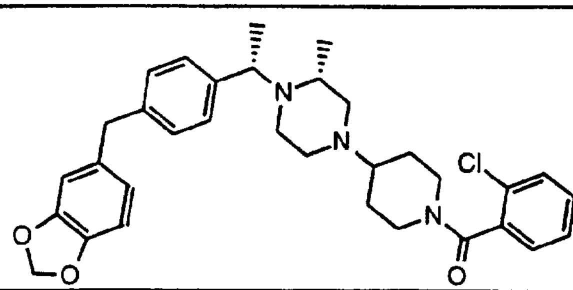
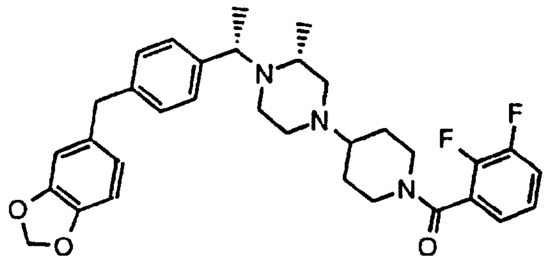
4 2		–
4 3		HRMS Calcd 575.2216 Found 575.2223
4 4		HRMS Calcd 589.2372 Found 589.2379
4 5		mp=255-257°C (dec)
4 6		FAB MH+=694
4 7		–

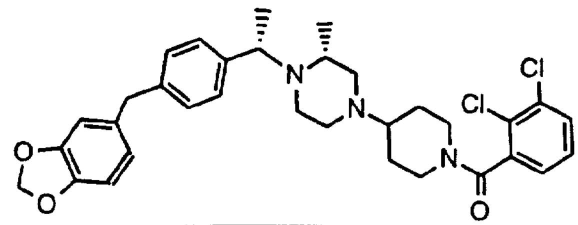
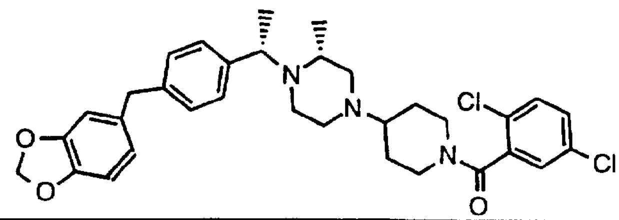
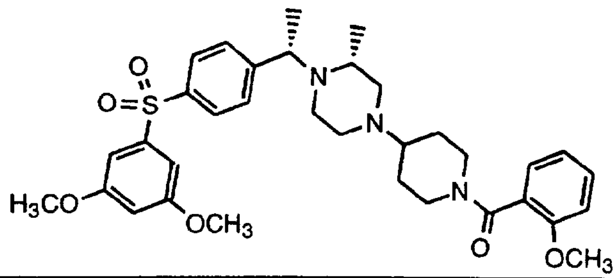
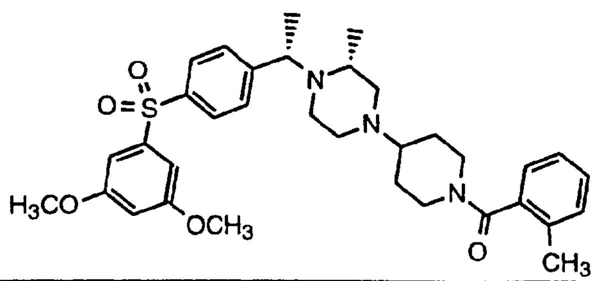
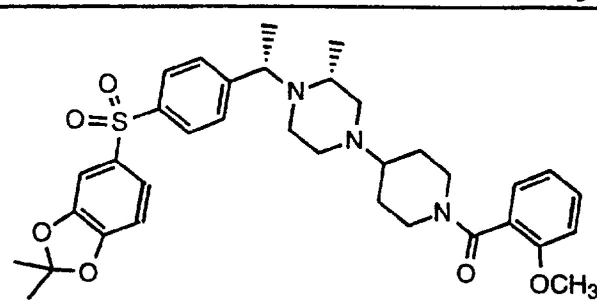
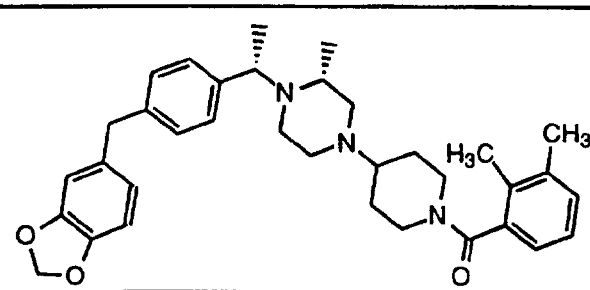
48		–
49		FAB MH+=632
50		mp=195-200°C (dec)
51		–
52		–
53		LRMS (FAB) Calc. for $C_{29}H_{38}O_8N_2S_2$ (M+H): 606 Found: 606

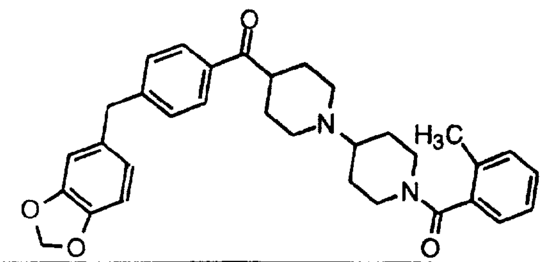
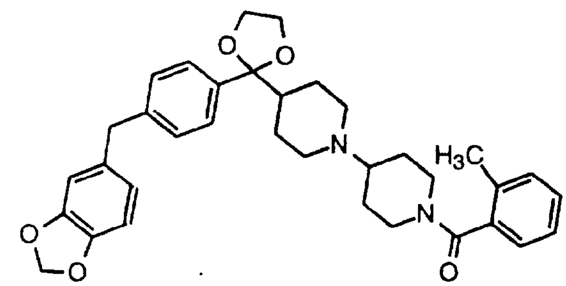
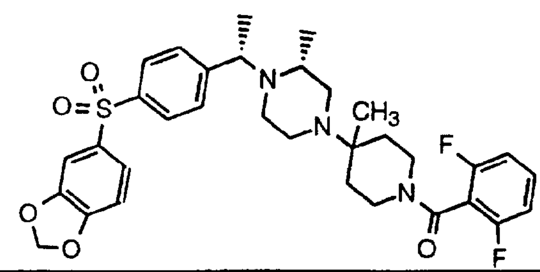
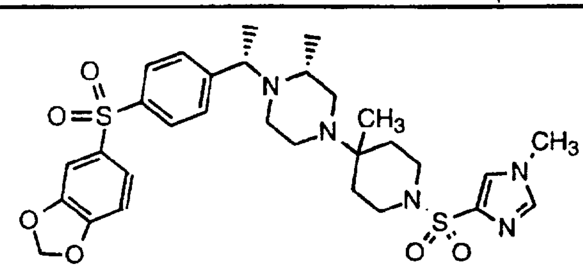
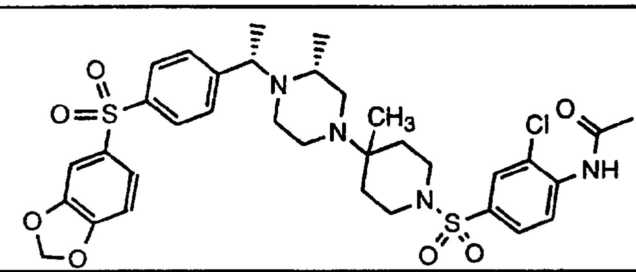
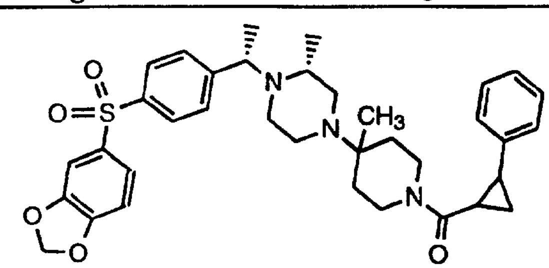
54		FAB (NBA-G/TG-DMSO): 590 (M+), 574, 406, 389
55		HRMS calcd 594.2672 found 594.2668
56		HRMS calcd 642.2686 found 642.2685
57		HRMS calcd 606.3002 found 606.2987
58		mp=218-220°C (dec)
59		mp=203-205°C (dec)

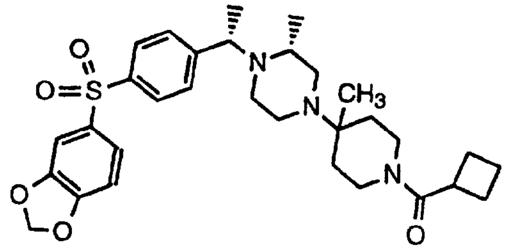
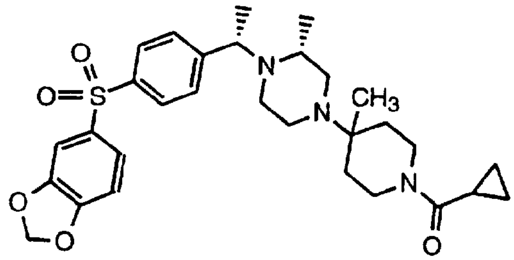
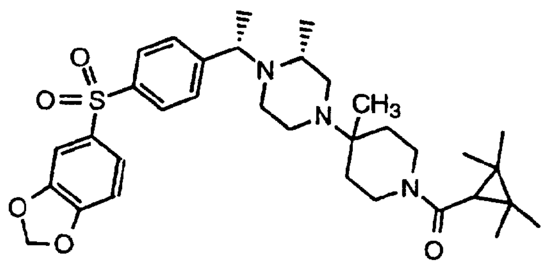
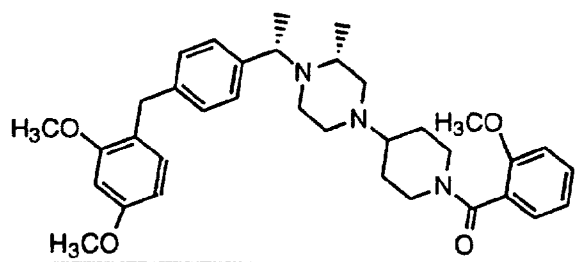
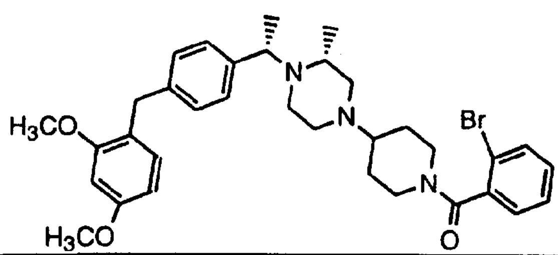
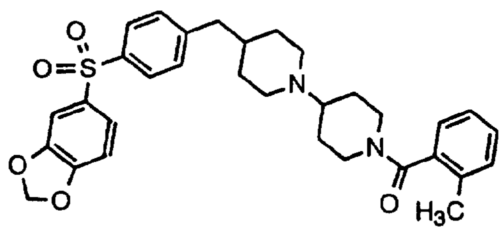
60		–
61		–
62		LRMS (FAB) Calc. for $C_{31}H_{40}O_8N_2S$ (M+H): 601 Found: 601
63		FAB MH+=682
64		HRMS calcd 636.3107 found 636.3119

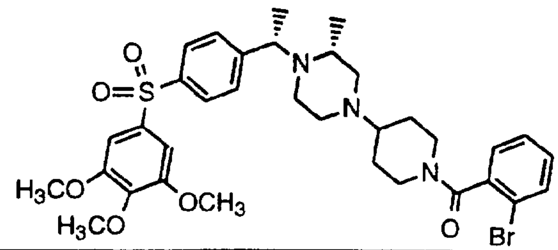
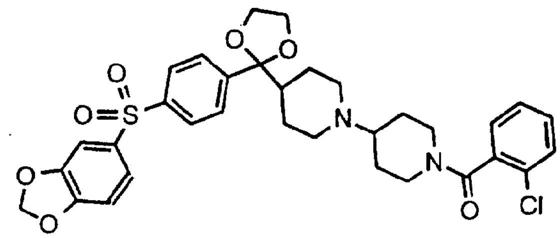
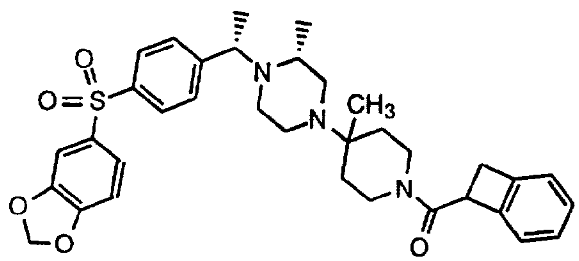
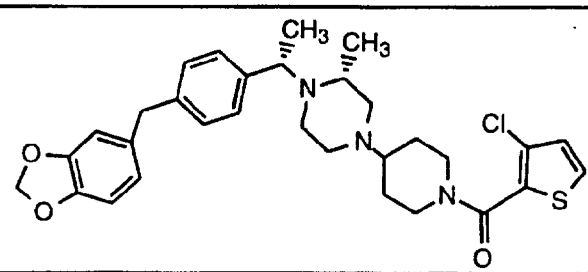
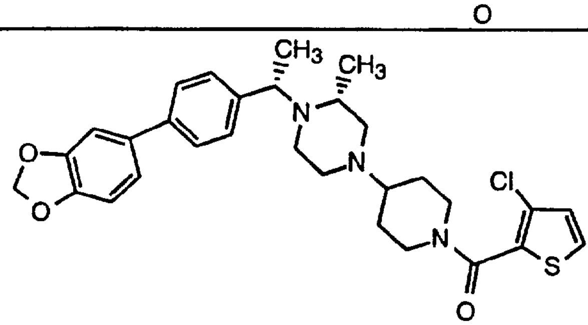
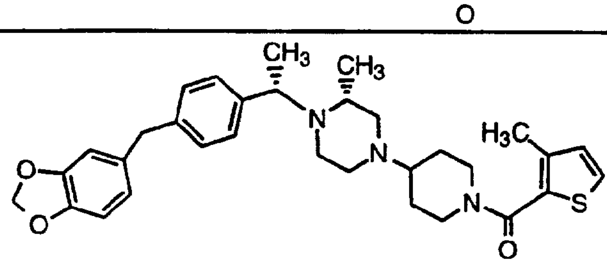
65		–
66		mp=157-160°C (dec)
67		FAB MH+=632
68		mp=172-175°C (dec)
69		
70		

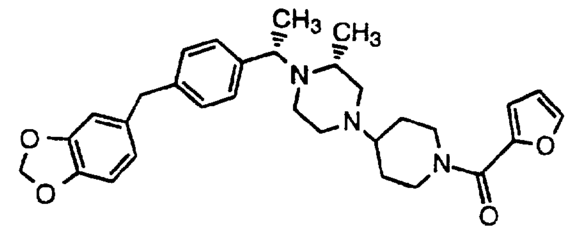
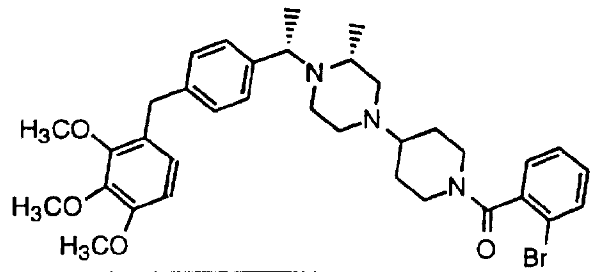
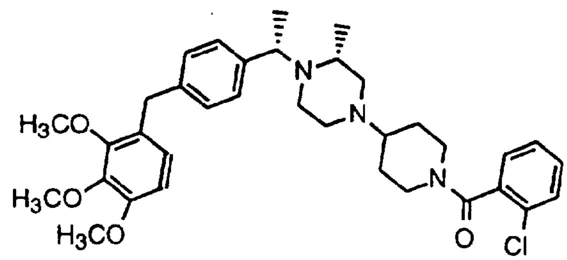
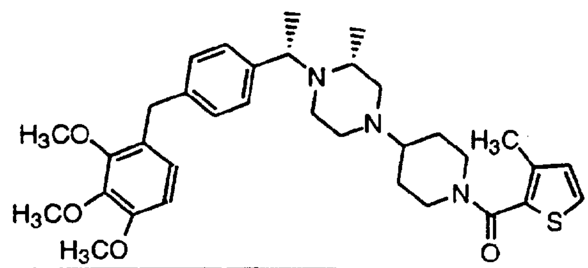
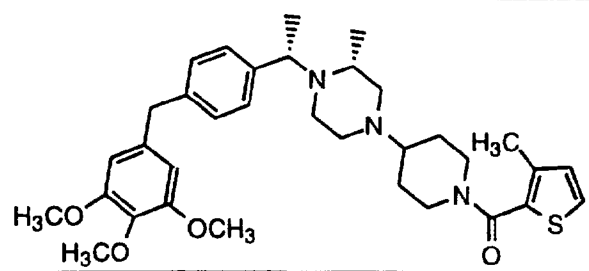
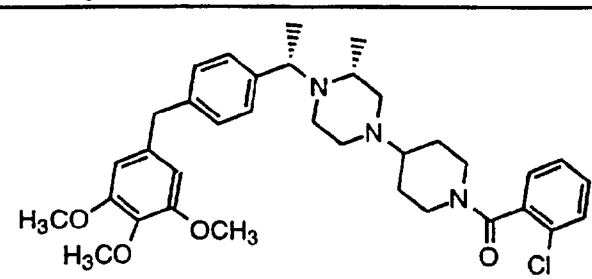
71		
72		
73		
74		
75		
76		

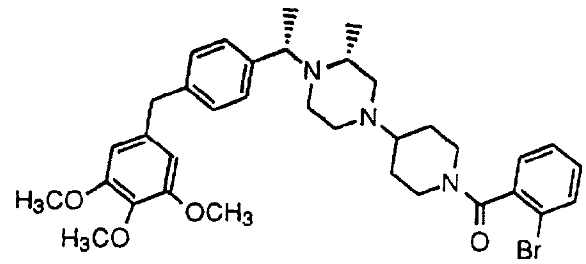
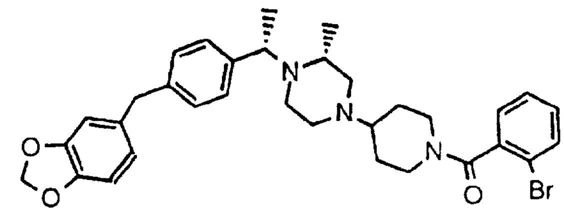
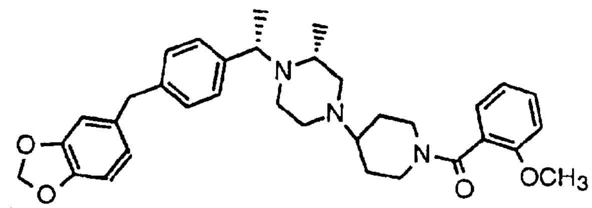
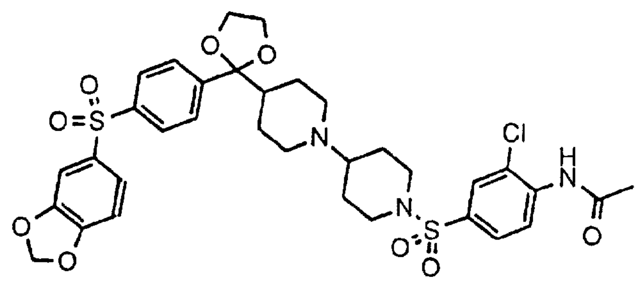
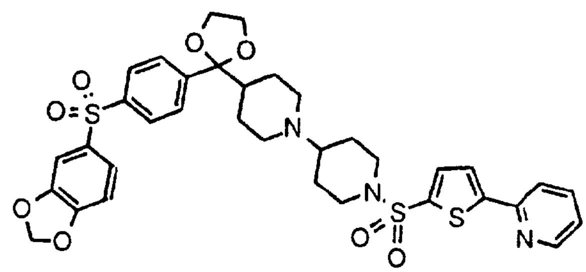
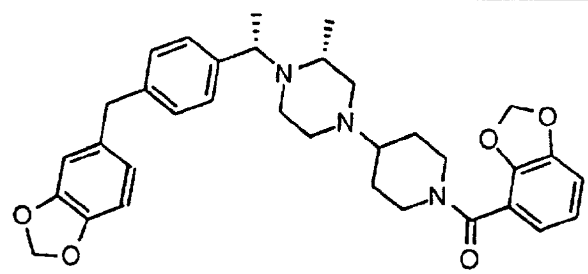
77		
78		
79		HRMS calcd 622.2951 found 622.2932
		HRMS calcd 606.3002 found 606.2999
81		HRMS calcd 634.2952 found 634.2962
82		mp: 207-212 °C (dec) Mass spectrum: MH+ = 554

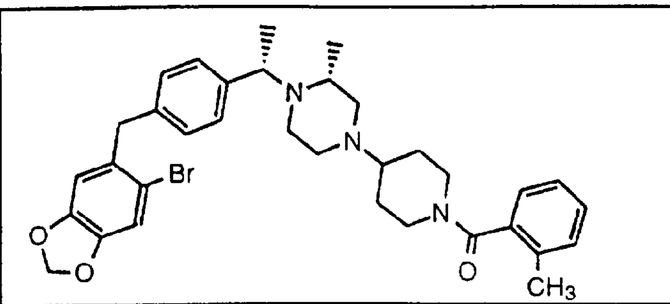
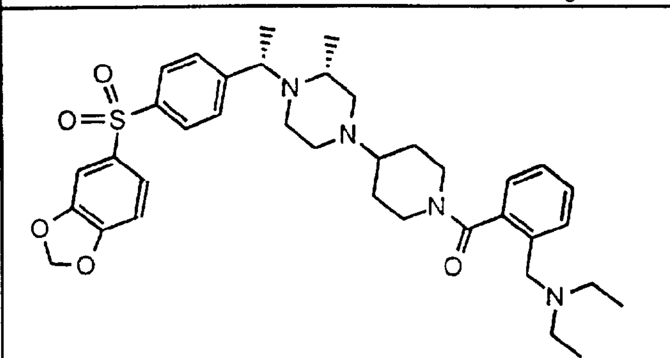
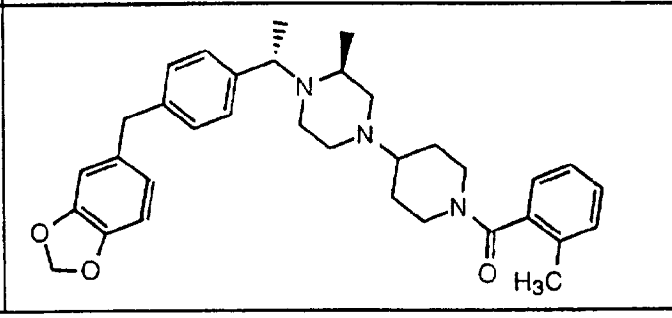
83		-
84		HRMS Calcd 579.3015 Found 569.3022
85		mp=242-245 (dec)
86		mp=206-209 (dec)
87		mp=237-239 (dec)
88		FAB (SIMS): 630 (M+), 391, 329, 307, 289

89		FAB (SIMS): 568 (M+), 391, 307, 232
90		FAB (NBA-G/TG-DMSO): 554 (M+), 538, 389, 289
91		FAB (NBA-G/TG-DMSO): 610 (M+), 594, 490, 426, 322
92		HRMS calcd 572.3488 found 572.3491
93		HRMS calcd 620.2488 found 620.2478
94		HRMS Calcd 561.2323 Found 561.2423

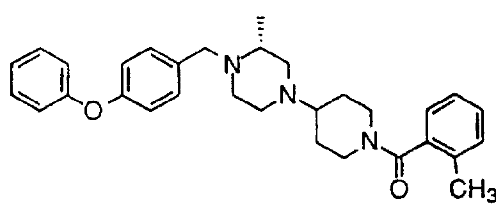
95		HRMS calcd 700.2056 found 700.2044
96		LRMS (FAB) Calc. for $C_{33}H_{35}O_7N_2SCl$ (M+H): 639 Found: 639
97		FAB (NBA-G/TG-DMSO): 616 (M+), 432, 389, 328
98		–
99		–
100		mp: 210-220°C (dec) Mass spectrum: MH+ = 546.

101		-
102		HRMS calcd 650.2593 found 650.2588
103		HRMS calcd 606.3099 found 606.3084
104		HRMS calcd 592.3209 found 592.3215
105		HRMS calcd 592.3209 found 592.3215
106		HRMS calcd 606.3099 found 606.3090

107		HRMS calcd 650.2593 found 650.2579
108		-
109		-
110		LRMS(FAB): M+H = 732
111		LRMS(FAB): M+H = 724
112		mp: 190-195 °C (dec) Mass spectrum: MH+ = 546.

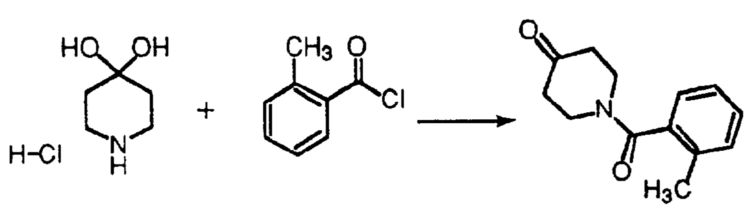
113		MH+ = 618, 620
114		mp=191°C (dec) MH+ = 611
115		MH+ = 540

Example 17



116

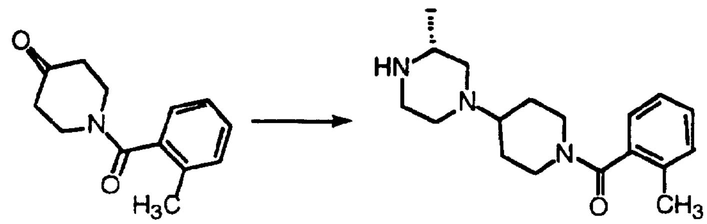
Step 1:



To a mixture of piperidone monohydratehydrochloride (27.5 g, 0.18 mol), K_2CO_3 (50g), 350 ml CH_2Cl_2, 250 ml water, cooled in an ice water bath, was added dropwise (over 1h) a solution of o-toluoyl

chloride (26 g, 0.17 mol) in 25 ml CH_2Cl_2. The mixture was warmed to room temperature and stirred overnight. The organic phase was separated, washed with water, dried over Na_2SO_4, filtered and concentrated on a rotarty evaporator. The crude product was purified on a silica column using hexane: EtOAc (4:1). Yield =93%

Step 2:

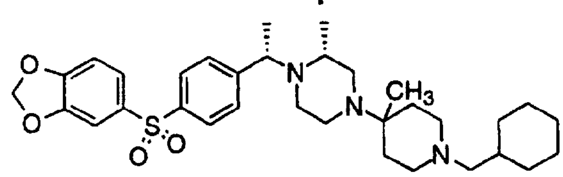


To a solution of 2-(R)-methylpiperazine (6.1 g, 61 mmol) in CH_2Cl_2 (250 ml) was added acetic acid (3.6ml), N-o-toluoylpiperidone (13.3 g, 61 mmol), and NaBH(OAc)3 (15.5 g, 73 mmol). The mixture was stirred overnight followed by dilution with CH_2Cl_2, washing with 10% Na_2CO_3 and water. Concentration of the organic phase was followed by purification on a silica column (CH_2Cl_2:CH_3OH = 20:1, sat'd with aq. NH_3). Yield = 50%

Step 3:

To NaBH(OAc)3 (0.042 g, 0.2 mmol) was added a solution of the product of Step 2 (0.03 g, 0.1 mmol), acetic acid (0.006 ml), and 4-phenoxy-benzaldehyde (0.1 mmol). The mixture was stirred overnight followed by dilution with CH_2Cl_2 (10 ml), washing with 10% Na_2CO_3, and drying over Na_2SO_4. Concentration of the organic phase was followed by purification on a silica column (EtOAc). The hydrochloride was prepared by dissolving the product in a minimum amount of EtOAc, followed by addition of anhydrous HCl. The precipitate was collected on a centrifuge and washed with Et_2O (3x), followed by drying under vacuum. Yield = 66%. M.p. 217-219°C (dec).

Example 18

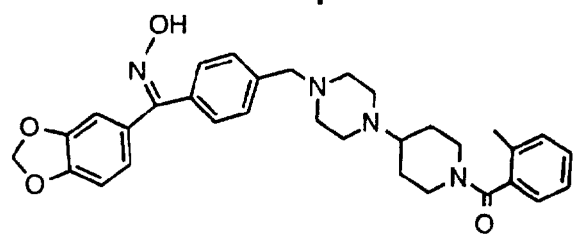


117

To NaBH(OAc)3 (0.026 g, 0.12 mmol) was added CH_2Cl_2 (1 ml), a solution of cyclohexanecarboxaldehyde (0.125 ml, 1M), acetic acid

(0.004 ml), and intermediate (20) of Example 9 (0.03 g, 0.06 mmol). The mixture was stirred overnight followed by dilution with CH_2Cl_2 (10 ml), washing with 10% Na_2CO_3 and drying over Na_2SO_4. Concentration of the organic phase was followed by purification on a silica column (EtOAc). The hydrochloride was prepared as described in Example 17. Yield=67%. M.p. 208-209°C (dec).

Example 19

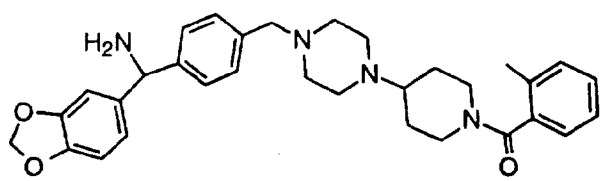


118

160 mg. of compound 28 were taken up in 4 ml ethanol with 45 mg of $H_2NOH{\bullet}HCl$. 2 ml of pyridine were added and the mixture was heated to reflux for 5 hours. The solvent was removed *in vacuo*, and the reaction was diluted with CH_2Cl_2 and extracted with aqueous $NaHCO_3$. The organic layers were dried over $MgSO_4$, evaporated, and the residue purified by column chromatography in a gradient of CH_3OH/EtOAc. This gave 130 mg of product as a mixture of *syn* and *anti* isomers.
FAB (MH+) = 541.

Examples 20A and 20B

20A:

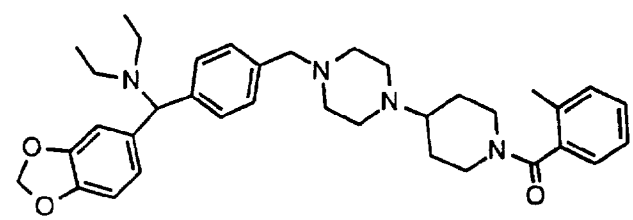


119

1.1 g of the product of Example 19 were taken up in 15 ml CH_2Cl_2 with 2 eq. of Et_3N, and cooled to -78°C under N_2. 440 mg (1.1 eq.) of chlorodiphenylphosphine were taken up in 2 ml of CH_2Cl_2 and added slowly to the reaction at this temperature. The reaction was stirred for 2 h in the cold and allowed to come to room temperature overnight. The solvent was removed *in vacuo*, and the crude material was taken up in 20 ml THF. 100 mg (excess) $NaBH_4$ was added and the mixture was stirred for 16 h at room temperature. The solvent was removed *in vacuo*, and the crude product was dissolved in a mixture of 10 ml of 6N HCl and

30 ml of CH_3OH. This mixture was stirred overnight at room temperature. The CH_3OH was evaporated from the mixture, and the reaction was taken to pH 9 with the addition of aqueous NaOH. This solution was extracted with CH_2Cl_2 and the organic layers washed with water, dried over $MgSO_4$ and evaporated to a crude oily product. This was purified by column chromatography in a gradient of CH_3OH/EtOAc to give 356 mg of amine product. MS (FAB): 527.5 (M+1), 510.5

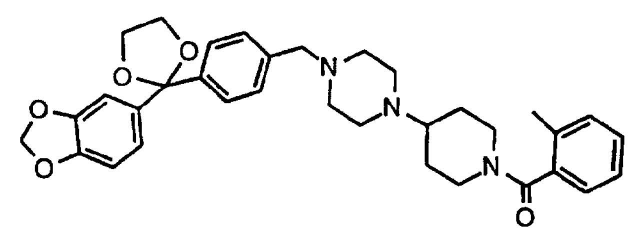
20B:



<u>120</u>

25 mg of the product of Step 20A were taken up in 2 ml CH_2Cl_2 with 90 mg of sodium triacetoxyborohydride. 9 microliters of acetaldehyde were added, and the mixture was stirred at room temperature for 1.5 hours. The reaction was diluted with additional solvent and extracted with aqueous $NaHCO_3$. The organic layers were dried over $MgSO_4$, evaporated, and purified by preparative thin-layer chromatography in 5% CH_3OH/EtOAc. This gave 12 mg of the desired product as an oil. FAB (M+) = 583.

Example 21

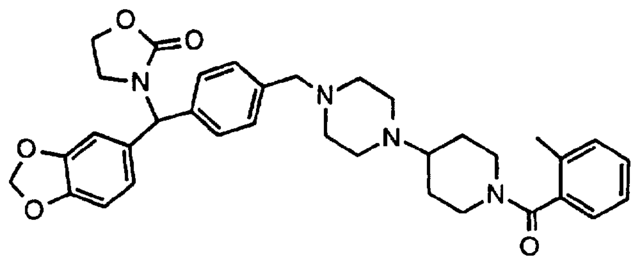


<u>121</u>

44 mg. of <u>28</u> were taken up in 20 ml of dry toluene with 2 ml of ethylene glycol and excess p-toluenesulfonic acid. The reaction was heated to reflux with a Dean-Stark water trap attached for 24 hours. NMR analysis showed partial reaction. Additional glycol and acid were added, and the reaction was heated an additional 24 hours. The mixture was extracted with aqueous $NaHCO_3$, evaporated, and purified by column chromatography in a gradient of CH_3OH/EtOAc to give 15 mg of

product, which still contains small amounts of the starting ketone.
MS (electrospray): 598 (M+1), 302.

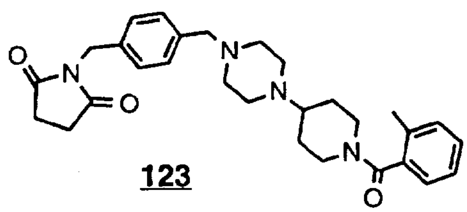
Example 22



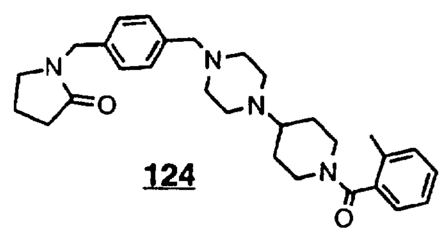
122

24 mg of compound **30** were taken up in 1 ml of CF_3CO_2H. An excess of 2-oxazolidinone was added and the mixture was stirred for 72 h at room temperature. Excess saturated $NaHCO_3$ solution was added, and the mixture was extracted with EtOAc. This was dried over Na_2SO_4, evaporated, and the residue purified by column chromatography in 5% CH_3OH/EtOAc to give approx. 15 mg of product as an oil.
MS (electrospray): 625.2 (M+1), 302.

Example 23

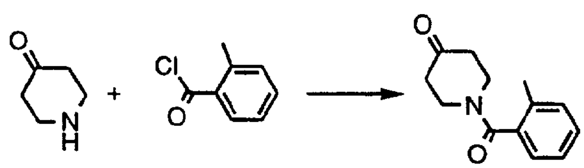


123



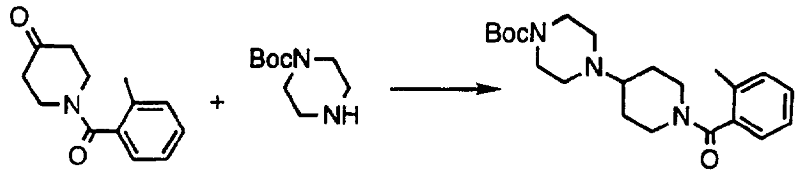
124

Step 1:



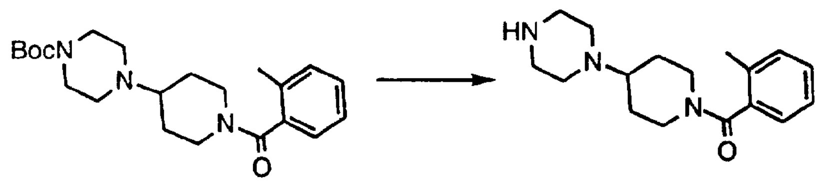
11 g of piperidinone hydrochloride were stirred in 100 ml CH_2Cl_2. 100 ml of 20% aqueous K_2CO_3 solution were added with vigorous stirring, followed by 8.8 ml of ortho-toluyl chloride. The mixture was stirred overnight at room temperature. The organic layer was separated and the aqueous layer was washed with additional solvent. The combined CH_2Cl_2 layers were dried over Na_2SO_4, evaporated, and purified by column chromatography in a gradient of hexane/EtOAc to give the product as an oil that solidified on standing.

Step 2:



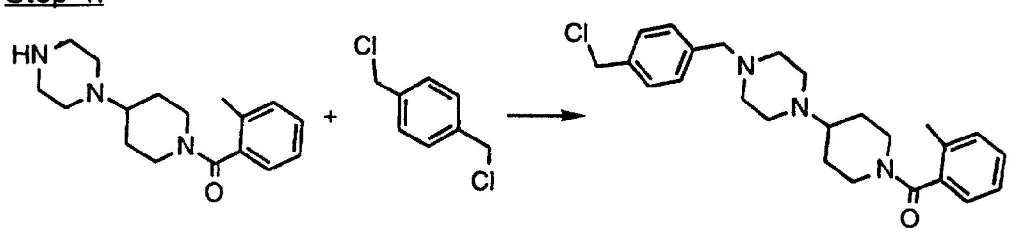
5.55 g of the product of Step 1 were combined with 4.75 g (1 eq.) of N-(t-butoxycarbonyl)piperazine in 100 ml of CH_2Cl_2. Sodium triacetoxy-borohydride (5.4 g) was added and the reaction was stirred at room temperature for 72 hours. An additional gram of sodium triacetoxy-borohydride was added, along with 2 ml of acetic acid, and the mixture was stirred an additional 24 hours. 25 ml of CH_3OH was added and the mixture was evaporated. The crude material was dissolved in CH_2Cl_2 and extracted with water. The organic layer was dried over Na_2SO_4, evaporated, and the residue purified by column chromatography in a gradient of EtOAc/hexane to give 6.7 grams of product.

Step 3:



6.7 g of the product of Step 2 were taken up in 100 ml CH_2Cl_2, and 20 ml of CF_3CO_2H were added slowly at room temperature. The reaction was stirred for 24 hours. 20 ml of water were added and the reaction was brought to pH 10 by the slow addition of solid NaOH. The organic layers were separated and the aqueous layers washed with additional CH_2Cl_2. The organic layers were dried over Na_2SO_4 and evaporated to give 5.1 g of product as a solid, which was used directly.

Step 4:



3.9 g of the product of Step 3 were taken up in 200 ml THF with 7.15 g (3 eq.) of 1,4-(bis)-chloromethylbenzene and 2 ml (1 eq.) of Et_3N. The mixture was heated to reflux for 7 hours and cooled to room

temperature. 300 ml of Et_2O were added and the precipitated $Et_3N{\bullet}HCl$ was removed by filtration. 34 ml of 1M HCl in Et_2O (2.1 eq.) was added in portions, with stirring, and the precipitate was filtered off and dried in vacuo to give 5.6 g of the dihydrochloride salt of the product, slightly contaminated with $Et_3N{\bullet}HCl$.

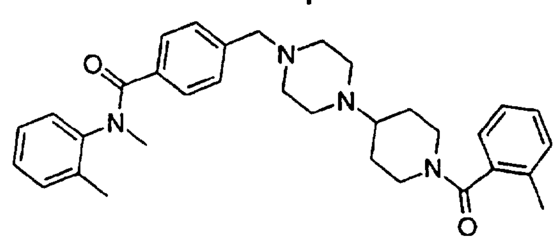
Compound **123**:

65 mg of the product of Step 4 (as a mixture containing 60% $Et_3N{\bullet}HCl$) were taken up in 2 ml dry DMF with excess K_2CO_3. The mixture was stirred for 1 h at room temperature until the solid starting material had dissolved. In a separate flask, excess succinimide was reacted with NaH in 1 ml dry DMF for 30 min. at room temperature. The DMF solution of the free amine was removed from the K_2CO_3 and added to this anion, and the mixture was stirred for 16 h at room temperature. Water was added, and the mixture was extracted twice with EtOAc. The organic layers were washed with water, dried over Na_2SO_4 and evaporated. This gave the product in sufficient purity to form its HCl salt directly. MS (electrospray): 489.1 (M+1), 276.

Compound **124**:

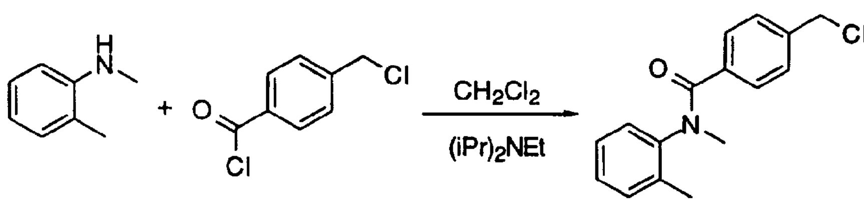
In a manner similar to that described for compound 123, but using pyrrolidinone in place of succinimide and potassium hexamethyl-disilazide (KHMDS) (in toluene) in place of NaH, compound **124** was prepared in sufficient purity to form its HCl salt directly.
MS (electrospray): 475 (M+1), 408.

Example 24:



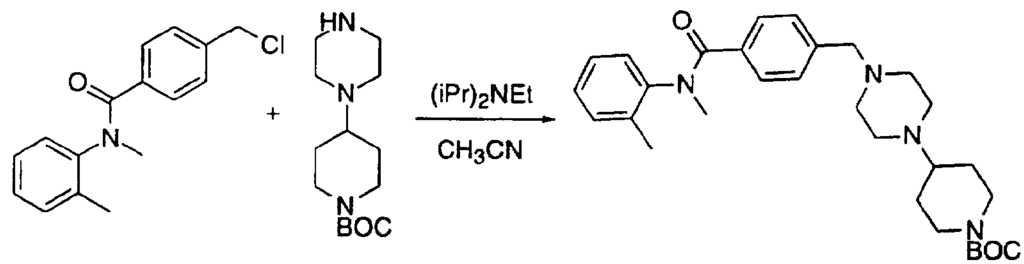
125

Step 1:



0.8 ml (6.35 mmol) of N-methyl-o-toluidine, 1.0 g (5.29 mmol) of 4-chloromethyl(benzoyl chloride) and 1.4 ml (7.93 mmol) of $(iPr)_2NEt$ were taken up in CH_2Cl_2 (20 ml) at 0°C. The solution was warmed to r.t., stirred at r.t. for 17 h, then was diluted with CH_2Cl_2 and washed with 1M HCl(aq.). The aqueous layer was washed with CH_2Cl_2. The combined CH_2Cl_2 layers were dried over $NaSO_4$, filtered and concentrated to give the desired benzyl chloride as a light brown oil (1.55 g, quant.).

Step 2:



The product of Step 1 (1.45 g, 5.29 mmol), piperazine-piperidine Boc compound (1.42g, 5.29 mmol), and $(iPr)_2NEt$ (1.84 ml, 10.6 mmol) were taken up in CH_3CN (25 ml). The solution was heated at reflux for 2.75 h. The solution was partitioned between CH_2Cl_2 and 1 N NaOH (aq.). The aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried over Na_2SO_4. Filtration and concentration gave gave a tan foam (2.7 g). Purification via flash chromatography(15/1 CH_2Cl_2/MeOH, SiO_2) gave 2.26 g (84 %) of a colorless foam.

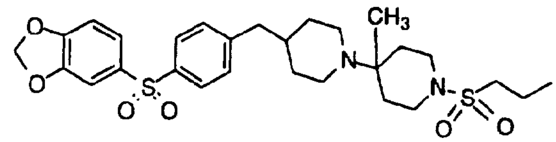
Step 3:

The BOC-protected product of Step 2 (2.26 g, 4.47 mmol) was taken up in CH_2Cl_2 (20 ml) and cooled to 0°C. TFA (5 ml) was added, and the solution was warmed to r.t. The solution was atirred at r.t. for 20 h. The solution was concentrated and the residue triturated with CH_2Cl_2/Et_2O to give a white solid. The solid was washed with Et_2O and dried, which gave 4.1 g (99 %) of the TFA salt of the amine.

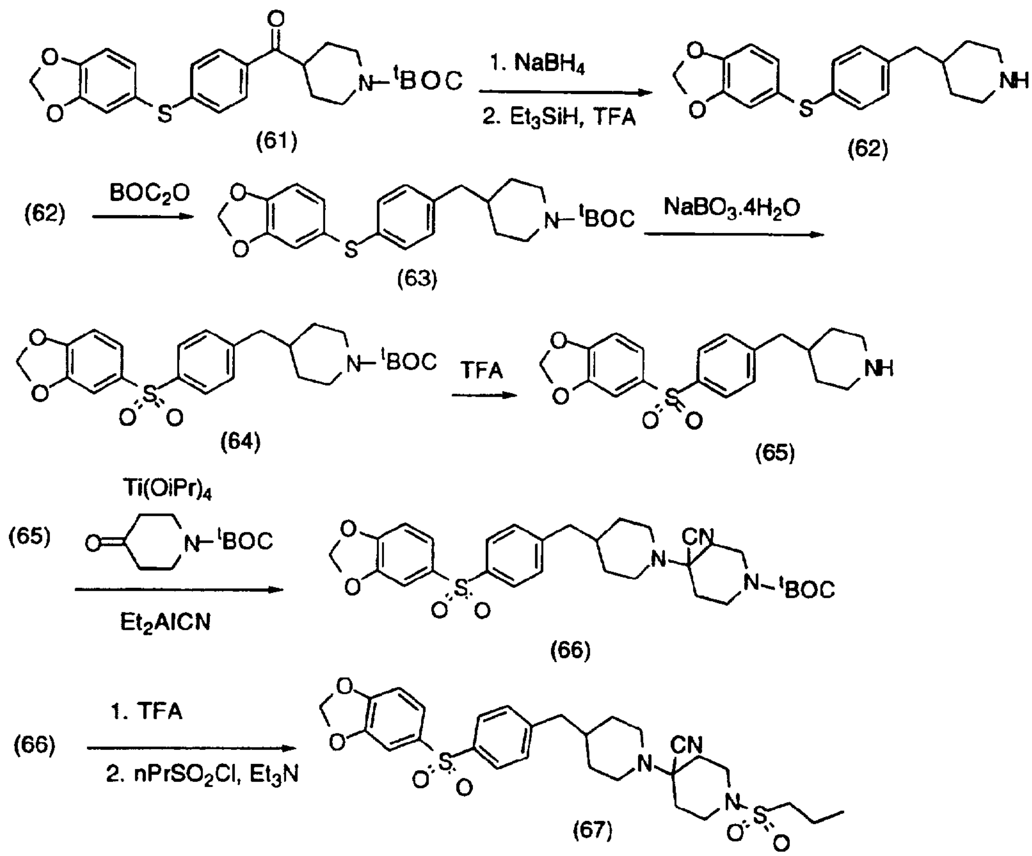
Step 4:

Using a procedure similar to that described in Example 1, treat the product of Step 3 to obtain **125**. M.p. = 235 - 240°C. HRMS (FAB) calc'd for $C_{33}H_{41}N_4O_2$ (MH): 525.3230. Found: 525.3239.

Example 25



126



Step 1: To a stirred solution of 10.0 g (22.6 mmol) of (61) in 50 ml of anhydrous CH_3OH was added $NaBH_4$ in portions at 0°C. The mixture was stirred at rt for 30 min and then quenched with water. The aqueous layer was extracted with (4x30 ml) EtOAc. The combined layers were dried over Na_2SO_4, filtered and concentrated to give 10.0 g (99%) of an alcohol which was used directly. To a stirred solution of the alcohol 10.0 g (22.5 mmol) in CH_2Cl_2 (100 ml) was added 16 ml of Et_3SiH, followed by 40 ml of TFA. The mixture was stirred at rt for 3 h and then quenched with 1N NaOH. The aqueous layer was extracted with CH_2Cl_2 (100 ml). The combined organic layers were dried over Na_2SO_4 and concentrated to yield 6.0 g (82%) of (62) as a colorless oil.

Step 2: To a stirred solution of (62) (5.0 g,15.29 mmol) in Et_2O (200 ml) and 40 ml of 10% NaOH was added BOC_2O. The mixture was then stirred at rt for 24 h. The layers were separated and the organic layer washed with water, dried (Na_2SO_4), filtered, concentrated and chromatographed to yield 5.7 g (87%) of (63) as colorless oil.

Step 3: To a stirred solution of (63) (5.7 g, 13.34 mmol) in acetic acid was added $NaBO_3{\bullet}4H_2O$ and stirred for 24 h at rt. The reaction mixture was then quenched with 25% NaOH. The organic layer was then extracted with EtOAc (3x30 ml). The combined organic layers were dried (Na_2SO_4), filtered, concentrated and chromatographed to yield 2.8 g (46%) of (64).

Step 4: To a stirred solution of (64) (1.5 g, 3.26 mmol) in CH_2Cl_2 (35 ml) was added TFA (2 ml). The mixture was stirred at rt for 1 h and concentrated. The residue was then diluted with CH_2Cl_2 and washed with 10% NaOH. The extracts were dried (Na_2SO_4), filtered and concentrated to yield 0.983 g (84%) of (65).

Step 5: To a stirred solution of (65) (0.983 g, 2.73 mmol) and t-butoxy-carbonyl piperidine (0.571 g, 2.87 mmol) in CH_2Cl_2 (3 ml) was added $Ti(iOPr)_4$ (1 ml). The reaction mixture was stirred at rt for 24 h and to the resulting solution was added 1.0 M toluene solution of Et_2AlCN (8.7 ml). The reaction was the stirred at rt for 2 h, diluted with EtOAc (10 ml) and quenched with water (3 ml). The resulting slurry was then filtered through celite, concentrated and chromatographed to yield 1.1 g (74%) of (66).

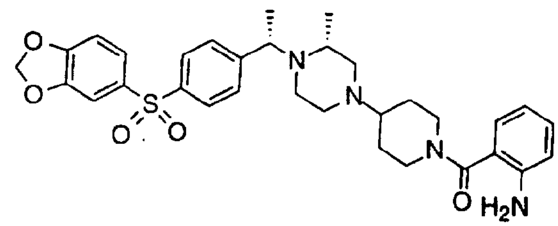
Step 6: To a stirred solution of (66) (0.225 g, 0.398 mmol) in CH_2Cl_2 was added TFA (1 ml). The mixture was stirred at rt for 1 h and concentrated. The residue was then diluted with CH_2Cl_2 and washed with 10% NaOH. The extracts were dried (Na_2SO_4), filtered and concentrated to yield crude amine which was used directly in the next step without purification 0.164 g (89%).

To a stirred solution of crude amine (0.053 g, 0.115 mmol) in CH_2Cl_2 (1 ml) was added Et_3N (0.100 ml) followed by n-$PrSO_2Cl$ (0.05 ml) and stirred at rt for 1 h. The reaction was quenched with 2N NaOH and the organic layer was extracted with CH_2Cl_2. The combined

organic layers were dried ($NaSO_4$), filtered, concentrated and chromatographed to afford 0.025 g (50%) of (67).

Step 7: To a stirred solution of (67) (0.018 g, 0.031 mmol) in THF (2 ml) was added 3.0 M solution of MeMgBr in Et_2O dropwise at rt. The reaction was the stirred for 2 h at rt and quenched with H_2O. The aqueous layer was then extracted with EtOAc, dried (Na_2SO_4), filtered, concentrated and chromatographed to yield 0.010 g (60%) of **126**. LRMS: calc'd: 562; found ($M+H^+$) 563.

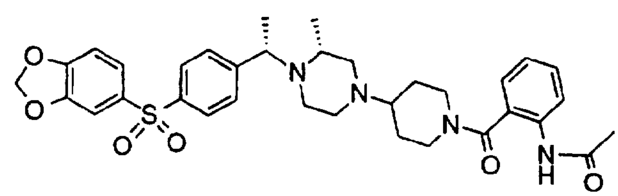
Example 26



127

Intermediate (1) (0.029 g) was dissolved in pyridine (0.1 ml) and isatoic anhydride (0.044 g) was added. The reaction solution was stirred for 48 h at room temperature then diluted with EtOAc (10 ml), washed with water, dried over $MgSO_4$, filtered and evaporated to give a solid. The acetone-soluble portion of this solid was purified by thin layer chromatography (silica gel adsorbent; 95:5 EtOAc:Et_3N eluant) to give a light colored foam (0.029 g) in 65% yield. MP (of hydrochloride): decomp >205°C

Example 27

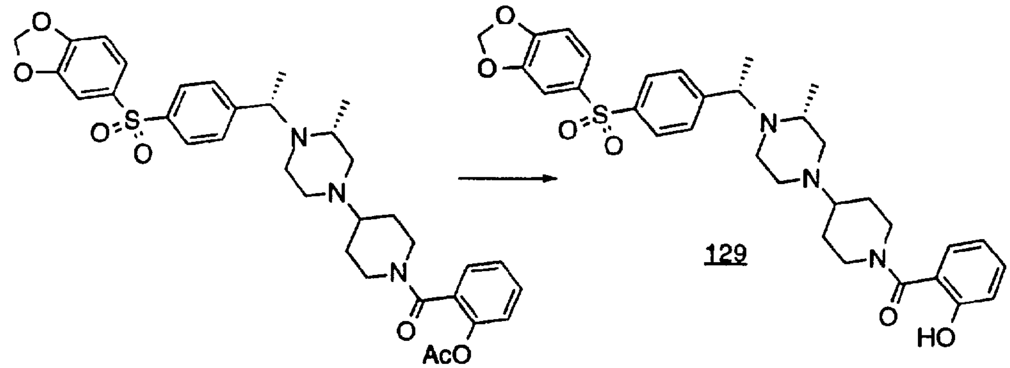


128

To a solution of **127** (0.096 g) and CH_2Cl_2 (0.32 ml) was added pyridine (0.01ml), acetic anhydride (0.02 ml) and N, N-dimethyl aminopyridine (4.8 mg). The resulting solution was stirred for 1.5 h, water (0.4 ml) was added and the mixture was extracted with CH_2Cl_2 (3 X 1 ml). The organic extract was dried over $MgSO_4$, filtered and evaporated to give a solid residue which was purified by thin layer chromatography (silica gel adsorbent; 9:1 CH_2Cl_2:CH_3OH eluant) to

give light colored foam (0.036 g) in 37% yield. MP (of hydrochloride): decomp >181°C.

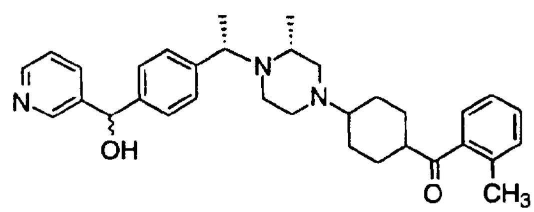
Example 29



129

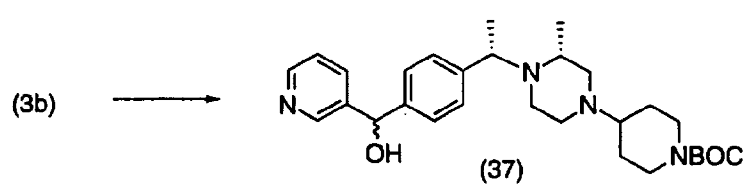
To a solution of the acetate shown above (prepared as described in Example 1) (0.071 g), and CH_3OH (0.32 ml) was added Et_3N in three portions, over a 3 h period (0.06 ml total). The resulting solution was stirred 3 days at room temperature, water was added and the solution was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered and evaporated to give the product (0.075 g) in 100% yield. M.p. (of hydrochloride): decomp >130°C.

Example 29



130

Step 1:



(37)

To a cooled (-78°C) solution of intermediate (3b) (0.41 g; 0.88 mmol) and THF (4.2 ml) was added nBuLi (0.34 ml of a 2.7 M solution in heptane) and the resulting solution was stirred for 3 min. Pyridine-3-uocarboxaldehyde was added as a solution in THF (0.17 ml in 2 ml, respectively) dropwise, over 1.5 min. The solution was stirred for 10 min at low temperature, 40 min at room temperature, poured into water,

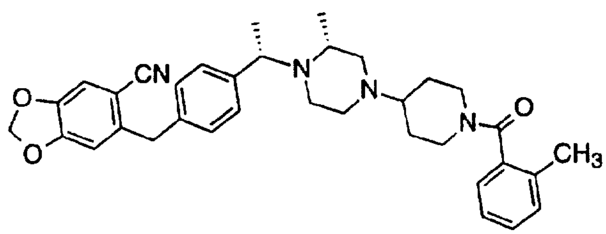
extracted with EtOAc, washed with brine and dried over $MgSO_4$. After filtration and evaporation, the resulting crude yellow oil was chromatographed on silica gel (77 g), eluting with 76:19:5 EtOAc: hexanes:Et_3N. Evaporation of the appropriate fractions gave, as a diastereomeric mixture of carbinols, (37) as a clear oil (0.28 g) in 64% yield. HRMS: MH^+: $C_{29}H_{43}N_4O_3$: calc'd: 495.3335; found: 495.3319.

Step 2:

Treat the product of Step 1 with o-toluoyl chloride using a procedure similar to that described in Example 3 to obtain the desired compound **130**. MP (of hydrochloride): 174-177°C.

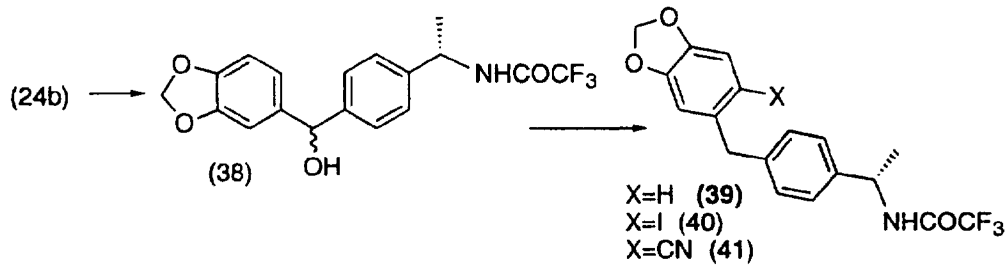
Examples 30A and 30B

30A:



131

Steps 1 to 4:



Step 1:

To a cooled (-78°C) solution of (24b) (17.9 g) and THF (170 ml) was added CH_3Li (43.2 ml of a 1.4 M solution in hexane) and the resulting solution was stirred for 10 min. N-BuLi (24.0 ml of a 2.5 M solution in hexane) was added and the resulting solution was stirred for 15 min. Piperonal was added as a solution in THF (9.6 g in 30 ml, respectively) dropwise and the cooling bath was removed. The solution was stirred for 15 min at room temperature, poured into dilute HCl and Et_2O and the Et_2O extracts were dried over $MgSO_4$. After filtration and evaporation, the resulting crude yellow oil was chromatographed on silica gel, eluting with 1:1 hexane:CH_2Cl_2 then 0→20 % Et_2O:CH_2Cl_2.

The fractions containing the desired product were combined and evaporated to give as a mixture of carbinols (38) (16.1 g) in 75% yield.

Step 2:

To a solution of (38) (15.8 g), CH_2Cl_2 (300 ml) and Et_3SiH (25 ml) was added TFA (25 ml). After 15 min at room temperature, the solution was washed with water, aqueous $NaHCO_3$, dried over $MgSO_4$ and filtered through a pad (20g) of silica, washing through the product with CH_2Cl_2. Evaporation and trituration with hexane (200 ml) gave, after filtration and drying, a white solid, (39) (13.9 g) in 92% yield. M.p.: 99-101°C.

Step 3:

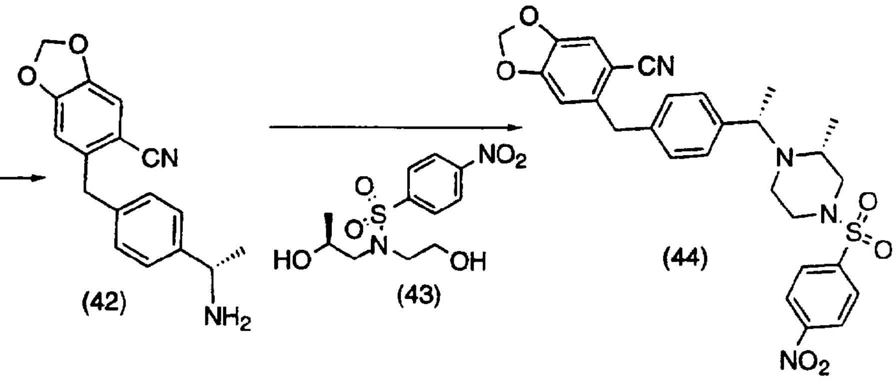
To a solution of (39) (2.23 g, 6.37 mmol), CH_2Cl_2 (23 ml) and iodine (1.84 g) was added, in one portion, silver trifluoroacetate (1.60 g). The resulting mixture was stirred for 1.5 h at room temperature, stored at 5°C for 14 h, diluted with CH_2Cl_2 (126 ml) and filtered. The resulting CH_2Cl_2 extract was poured onto a column of silica gel (63 g) and the product washed through with CH_2Cl_2. Any fractions containing a light pink color were washed with 10% $Na_2S_2O_3$ and dried, then combined with the other fractions and evaporated, to give (40) (2.86 g) as a white solid in 94% yield. M.p.: 125-127°C.

Step 4:

(40) (1.50 g, 3.14 mmol) was dissolved in N,N-dimethylacetamide (10 ml) and CuCN (0.94 g) and NaI (0.14 g) were added. The resulting mixture was degassed and heated at 110°C for 8 h. The mixture was cooled, diluted with CH_2Cl_2, filtered and the resulting solids were washed with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with 1:1 NH_4OH:H_2O (3X), water and brine, dried over $MgSO_4$, filtered, evaporated and applied to a silica gel column (55 g). After elution with hexanes (100 ml) and 4:1 hexanes:EtOAc, the desired fractions were evaporated to give a waxy white solid, (41), (1.10 g) in 94% yield. M.p.: 114-116°C.

Steps 5 and 6:

(41) ⟶



(42) (43) (44)

Step 5:

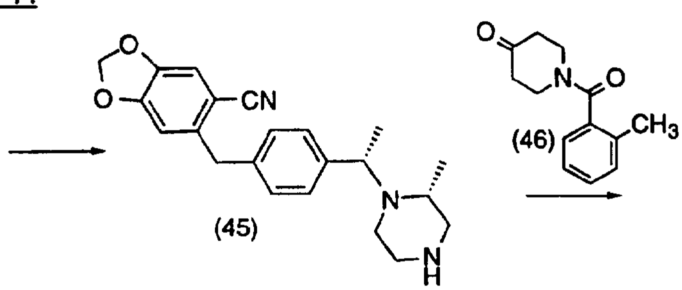
Treat (41) using a similar procedure to that described in Example 10, Step 3, to give the amine (42) as a white solid in 70% yield.
M.p.: 55-58°C

Step 6:

To a cooled (0°C) solution of diol (43) (0.88g), CH_2Cl_2 (29 ml) and Et_3N (1.21 ml) was added CH_3SO_2Cl (0.46 ml). The resulting solution was stirred at 0°C for 15 min and at room temperature for 1 h. The solution was poured into a mixture of CH_2Cl_2 and ice water, the CH_2Cl_2 layer was removed and washed with water, brine and dried over Na_2SO_4. After filtration and careful evaporation of the solvent, CH_3CN (2.30 ml) and iPr_2EtN (1.20 ml) and (42) (0.64 g) were added and the mixture was heated at 80°C for 12 h. The resulting solution was diluted with EtOAc, washed with 2 N NaOH, water and brine, dried over $MgSO_4$, filtered and evaporated to give a gold foam which was applied to a silica gel (91 g) column and eluted with 3:1 hexane:EtOAc, then 2:1 hexane:EtOAc. The desired fractions were combined and evaporated to give (44) (1.09 g) as a gold foam in 87% yield.
HRMS:MH^+: $C_{28}H_{29}O_6N_4S$: calc'd: 549.1808; measured: 549.1803.

Step 7:

(44) ⟶

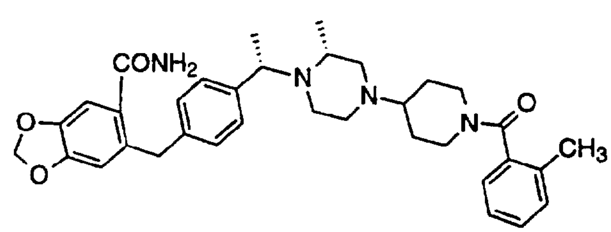


(45) (46) **131**

Part A: To a cooled (0°C) mixture of piperidone hydrate hydrochloride (27.5 g), CH_2Cl_2 (350 ml), K_2CO_3 (50 g) and water (250 ml) was added dropwise a solution of o-toluoyl chloride (22 ml) and CH_2Cl_2 (25 ml). After the addition was complete, the cooling bath was removed and the mixture was stirred for 24 h, the CH_2Cl_2 layer was removed, washed with water, dried over $MgSO_4$, filtered and evaporated to give a clear oil. The oil was chromatographed on silica gel (320 g), eluting with 4:1 hexane:EtOAc and the desired fractions were combined and evaporated. The resulting clear oil crystallized on standing to give a white solid, (46), (35.7 g) in 92% yield.

Part B: To a solution of (44) (0.21 g) and DMF (0.75 ml) was added PhSH (0.047 ml) and K_2CO_3 (0.15 g) and the resulting mixture was stirred for 28 h. The reaction mixture was diluted with EtOAc and water and 2 N NaOH (1.0 ml) were added. The aqueous layer was extracted with EtOAc (three portions), the EtOAc extracts were combined and washed with brine, dried over $MgSO_4$, filtered and evaporated to give 0.55 g of an oil (45) which was taken up in CH_2Cl_2 (0.55 ml) and acetic acid (9 µl). To this solution was added (46) (0.04 g) and $NaB(OAc)_3H$ (0.048 g). After stirring for 6 h, the reaction solution was partitioned between CH_2Cl_2 and 2 N NaOH. The CH_2Cl_2 layer was washed with water and brine, dried over $MgSO_4$, filtered, evaporated and applied to a thin layer silica plate. After elution with 2:1 CH_2Cl_2:acetone, the desired product, <u>131</u>, was collected as a foam (0.72 g) in 85% yield.
M.p. (hydrochloride): 165-167°C.

30B:

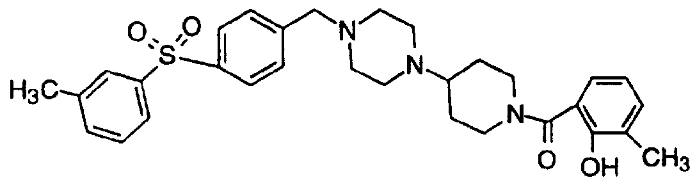


<u>**132**</u>

To a solution of <u>131</u> (0.029 g) and THF (0.5 ml) was added nBu_4NOH (0.085 ml) and 30% H_2O_2 (0.017 ml). More nBu_4NOH and H_2O_2 were added as described above after 3 h and 48 h then the reaction was stirred 3 h more after the last addition. The reaction was diluted with EtOAc, the aqueous layer was removed, extracted with

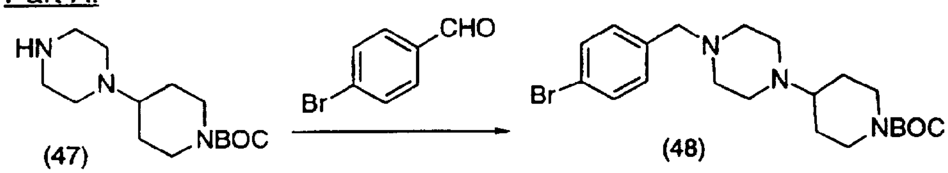
EtOAc (3X) and the EtOAc extracts were combined, washed with water and brine, dried over $MgSO_4$, filtered and evaporated to give a white crystalline solid which was further purified by chromatography (silica gel; 100 mg; 95:5 EtOAc:Et_3N eluant). The desired product was collected and evaporated to give a white solid, **132**, (10.5 mg) in 35% yield. M.p. (of hydrochloride): decomp >164°C.

Example 31



133

Part A:

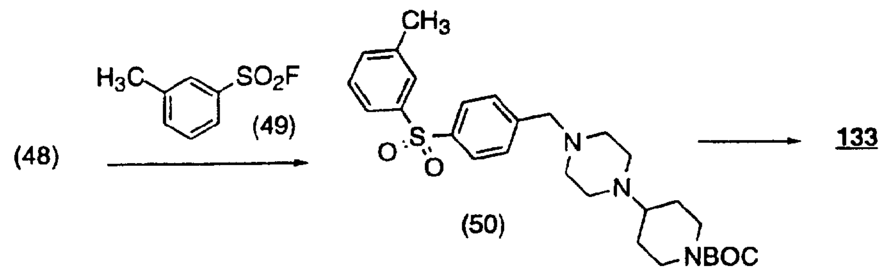


To a solution of piperazine (13 g), N-BOC 4-piperidone (10 g), CH_2Cl_2 (200 ml) and acetic acid (2.0 ml) was added $NaB(OAc)_3H$ (20 g) in four portions over 2 h. The mixture was stirred for 22 h, diluted with CH_2Cl_2 and added slowly to 1 N NaOH (250 ml). The aqueous layer was extracted with CH_2Cl_2 (3X), the CH_2Cl_2 extracts were combined, washed with water and dried over $MgSO_4$. The solution was filtered, concentrated and purified by silica gel chromatography (eluant: 8:1 CH_2Cl_2 :CH_3OH, then 10:5:1 CH_2Cl_2 :CH_3OH: NH_3(aq)). After evaporation of the solvent, (47) was collected as a white solid (7.18 g) in 53 % yield.

To a solution of p-bromo benzaldehyde (5.25 g), CH_2Cl_2 (100 ml) and (47) (8.72 g) was added $NaB(OAc)_3H$ (8.05 g) in 8 portions over 40 min. After stirring for 19 h, CH_2Cl_2 (20 ml) and $NaB(OAc)_3H$ (1.05 g) were added, the reaction mixture was stirred for 2 h, diluted with CH_2Cl_2, poured into 2 N NaOH and the aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with water and brine, dried over $MgSO_4$, filtered, evaporated and chromatographed on silica gel (250 g), eluting with 76:19:5 hexane:EtOAc:Et_3N. The desired fractions

were combined and evaporated to give (48) as a white solid (8.48 g) in 69 % yield. M.p.: 87-90°C.

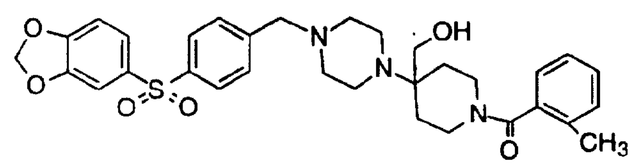
Part B:



To a solution of m-toluene sulfonyl chloride (13.2 g) and acetone (107 ml) was added a solution of KF (11 g) and water (87 ml), slowly dropwise. The resulting solution was diluted with EtOAc and the organic layer was removed. The aqueous layer was extracted with EtOAc, combined with the initial EtOAc extract, dried over $MgSO_4$, filtered and evaporated to give (49), (11.7 g) in 97% yield, which was used directly without further purification.

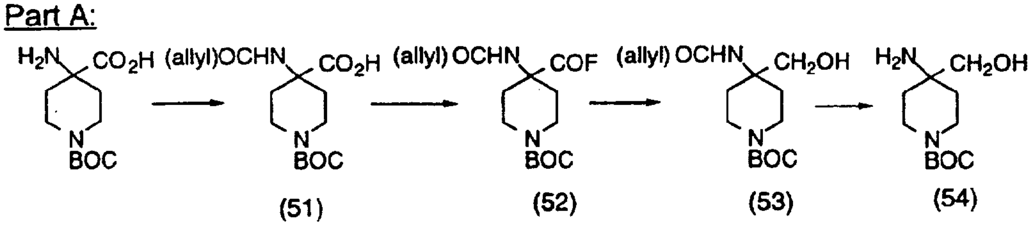
(50) was prepared using a procedure similar to Example 29, except (49) was used in place of 3-pyridine carboxaldehyde. Using procedures described in Example 1 (or Example 2), (50) was converted to **133**. M.p. (hydrochloride): decomp >227°C.

Example 32



134

Part A:



The amino acid (0.21 g), DME (15 ml) and 1 M NaOH (3 ml) were mixed and allyl chloroformate (0.2 ml) was added. The solution was stirred for 15 h, cooled to 0°C, acidified with 1 M HCl and extracted with EtOAc. The EtOAc extracts were washed with brine and dried over

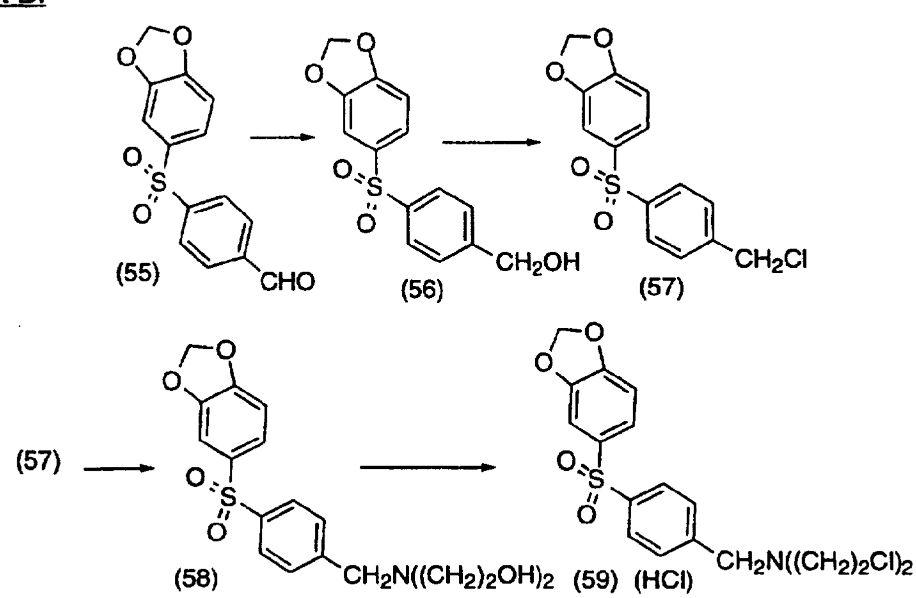
Na_2SO_4, filtered and concentrated to give (51) as a colorless foam, which was used directly in the next procedure.

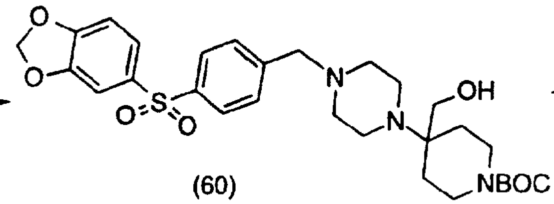
Cyanuric fluoride (0.41 g), (51) (0.50 g), pyridine (0.15 ml) and CH_2Cl_2 (15 ml) were mixed at 0°C. The mixture was stirred at 0°C for 3.75 h, diluted with CH_2Cl_2 and poured into cold water. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 extracts were dried over $MgSO_4$, filtered and concentrated to give crude (52) (0.50 g) as a thick oil, which was used directly in the next procedure.

The acid fluoride (52) (0.31 g) and CH_2Cl_2 (10 ml) were mixed and $NaBH_4$ (72 mg) was added followed by CH_3OH (0.9 ml), dropwise over 10 min. The reaction was stirred for 20 min at room temperature, poured into a separatory funnel containing 1 M HCl and EtOAc and the aqueous layer extracted with EtOAc. The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated to give (53) as an oil (0.30 g) in 51 % yield.

Palladium acetate (4 mg), 3,3',3"-phosphinidynetris(benzene sulfonic acid) sodium salt (20 mg), Et_2NH (1.3 g) and (53) (0.28 g) were mixed with CH_3CN (3 ml) and water (3 ml) and stirred for 3 h. The reaction mixture was co-evaporated with toluene (6 ml) to obtain (54), which was used directly in the next part.

Part B:



(59) $\xrightarrow{(54)}$  → **134**

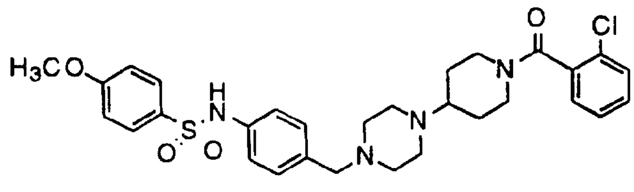
(60)

(55) (0.50 g) (prepared using the procedure of Example 1, using p-fluorobenzaldehyde) was taken up in CH_3OH (20 ml) and CH_2Cl_2 (10 ml), cooled to 0°C and $NaBH_4$ (80 mg) was added. After stirring for 2.5 h at room temperature, the solution was partitioned between EtOAc and 1 M HCl. The EtOAc layer was removed, the aqueous layer was extracted with EtOAc, the organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to give (56) (0.52 g) as a colorless oil. A solution of CH_2Cl_2, $SOCl_2$ (0.13 ml) and DMF (0.033 ml) was stirred for 4 h at room temperature and concentrated. The residue was co-evaporated with toluene (2x 20 ml) to give a yellow solid (57) (0.20 g) which was dissolved in CH_3CN (10 ml) and diethanolamine (0.24 g). After heating at reflux for 2 h, the reaction solution was partitioned between water and EtOAc, the EtOAc layer was removed, the aqueous layer was extracted with EtOAc, the organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered and evaporated to give the product (58) (0.26 g) as a colorless oil. This product was dissolved in 1,2-dichloroethane (5 ml), $SOCl_2$ (0.16 ml) was added and the resulting mixture was heated at reflux for 3 h. The volatile materials were removed in vacuo to give the product (59) as a thick gum, which solidified on storage at 5°C. This material (0.17 g) was mixed with (54) (0.10 g), NaI (0.20 g), CH_3CN (10 ml) and diisopropyl ethyl amine (0.45 ml) and the resulting mixture was heated at reflux for 3.5 h. The reaction solution was partitioned between water and EtOAc, the EtOAc layer was removed, the aqueous layer was extracted with EtOAc, the organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered and evaporated to give a brown oil. Purification on silica gel, eluting with 10:1 CH_2Cl_2 :CH3OH, gave (60) (77 mg) as an oil. HRMS:MH^+:$C_{29}H_{40}N_3O_7S$ calc'd: 574.2587; measured: 574.2580.

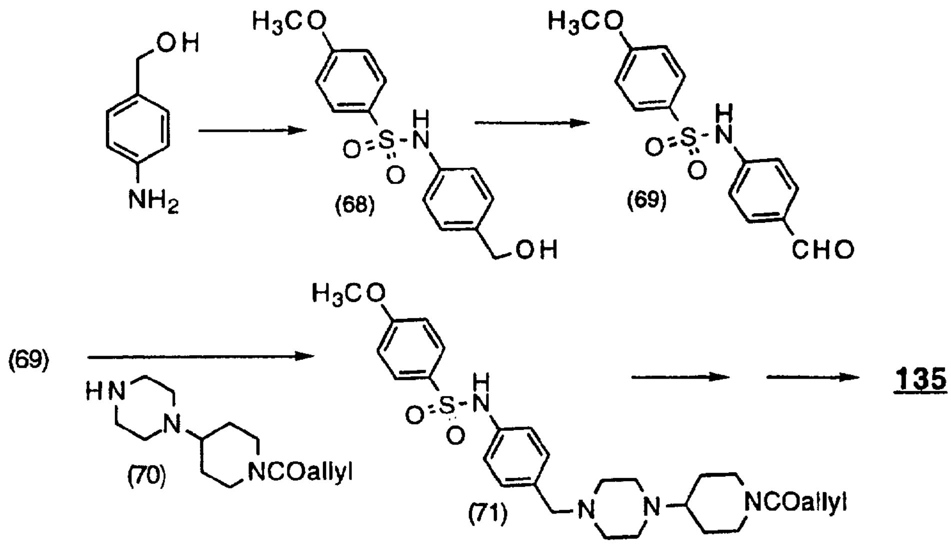
(60) (77 mg) was dissolved in 1 M HCl in CH_3OH (5 ml), stirred for 24 h, concentrated and the residue was taken up in CH_3OH and

triturated with Et_2O to give a white solid (59 mg). Using the procedure of Example 1, (60) was converted to **134**. HRMS (FAB) calc'd for $C_{32}H_{38}N_3O_6S$ (MH^+): 592.2481; found: 592.2467; m.p. 187-197°C.

Example 33



135



Step 1: To a cooled (-78°C) mixture of 4-amino benzyl alcohol (0.50 g), diisopropyl ethyl amine (1.41 ml) and CH_2Cl_2 (40 ml) was added TMSCl (0.52 ml). The resulting slurry was stirred at -78°C for 15 min and at 0°C for 1 h. The resulting solution was cooled to -78°C, p-methoxyphenyl sulfonyl chloride (0.84 g) was added, the cooling bath was removed and the reaction was stirred at room temperature for 15 h. The reaction solution was diluted with CH_2Cl_2 and water was added. The aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were dried over $MgSO_4$, filtered and evaporated to give a yellow oil, which was taken up in CH_3OH (20 ml) and K_2CO_3 (1.5 g) was added. The resulting mixture was stirred for 1 h., filtered through a plug of Celite, concentrated, taken up in EtOAc and washed with water. The aqueous layer was extracted with EtOAc, the combined organic extracts were dried over $MgSO_4$, filtered and evaporated to give a yellow oil (0.78 g), which was used without further purification in the next step.

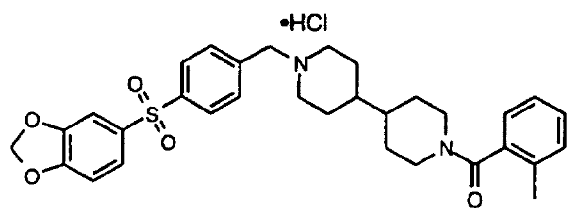
Step 2: (68) (0.47 g) and MnO_2 (3.0 g) were mixed with CH_2Cl_2 (20 ml) and stirred for 20 h. The solution was filtered through Celite and concentrated to give 0.30 g of a thick oil, (69), which was used directly in the next step.

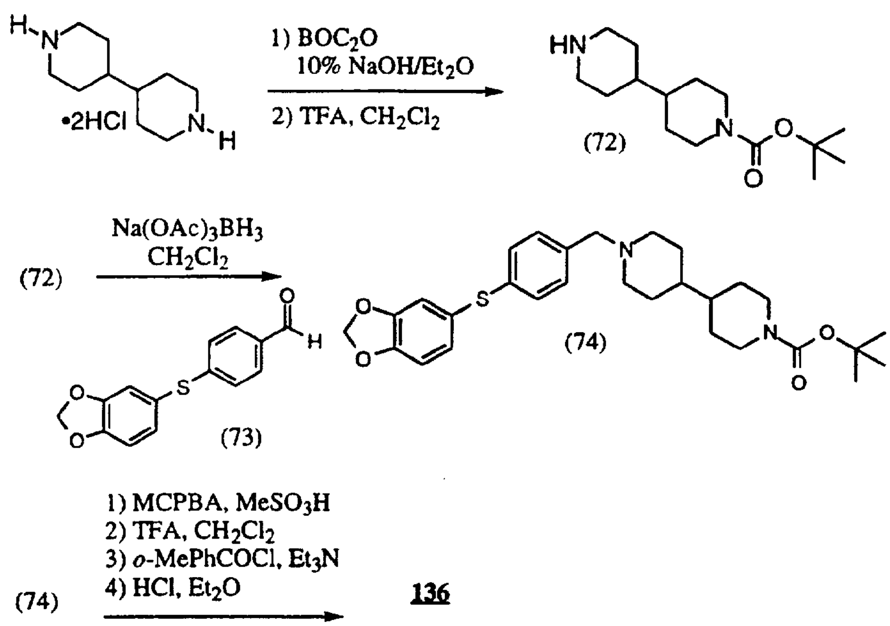
Step 3: Use a procedure similar to the second portion of Part A in Example 31, with intermediates (69) and (70) as the reactants. Crude (71) (0.30 g) was used directly in the next step.

Step 4: Treat (71) (148 mg) using a procedure similar to that in the last portion of Part A of Example 32 to obtain the corresponding brown crude amine, which was used directly in the next step.

Step 4: Using the procedure of in Example 1, treat (71) to obtain **135**. M.p. (with decompostion) 190-200°C.

Example 34





Step 1: To a stirred 0°C solution of 4,4'-bispiperidine hydrochloride (2.53 g, 10.5 mmol) in a 1:1 solution of Et_2O/10% aq. NaOH (26 ml) was added a 2.5 M solution of di-*tert*-butyldicarbonate in Et_2O (10 ml, 23.1 mmol) over 30 min with vigorous stirring. After stirring at room

temperature for 2 h, the mixture was poured into a separatory funnel, extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting product (3.00 g) was used without further purification.

The crude bispiperidine (2.74 g, 7.44 mmol) was dissolved in CH_2Cl_2 (50 ml) and TFA (0.57 ml, 7.44 mmol) was added to the solution. The reaction stirred at room temperature and monitored by TLC. After two more equivalents of TFA were added, the reaction was approximately a 1:2:1 mixture of starting material, (72), and 4,4'-bispiperidine. The mixture was diluted with CH_2Cl_2, washed with 1N NaOH, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (10/90 CH_3OH/CH_2Cl_2, then 5/10/85 $NH_4OH/CH_3OH/CH_2Cl_2$) yielded 1.00 g of (72) (53% yield).

<u>Step 2</u>: To a solution of (73) (480 mg, 1.85 mmol) in CH_2Cl_2 (7.4 ml) was added (72) (520 mg, 2.04 mmol) and sodium triacetoxyborohydride (590 mg, 2.78 mmol). The reaction was stirred for 12 h at room temperature under N_2. The mixture was quenched with $NaHCO_3$ (sat), extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated under reduced pressure, yielding (74) (880 mg, 94% yield).

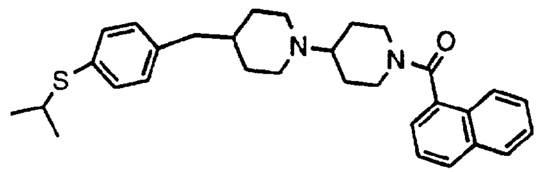
<u>Step 3:</u> To a solution of (74) (880 mg, 1.72 mmol) in CH_2Cl_2 (8.6 ml) was added CH_3SO_3H (0.17 ml, 2.58 mmol) in CH_2Cl_2 (4.7 ml). After cooling to 0°C with stirring, 60% MCPBA (1.04 g, 3.61 mmol) in CH_2Cl_2 was added dropwise. The reaction was stirred for 1 h at room temperature under N_2. The mixture was washed with $Na_2S_2O_3$ (sat), 1 N NaOH, and H_2O, dried over $Na2SO_4$, filtered, and concentrated to yield 0.93 g of the sulfone (100% yield).

The sulfone (0.93 g, 1.71 mmol) was dissolved in CH_2Cl_2 (11.4 ml) and TFA (2.6 ml, 34.2 mmol) was added. The reaction was stirred for 2 h at room temperature under N_2. The mixture was diluted with CH_2Cl_2, washed with 1N NaOH, filtered, and concentrated under reduced pressure, yielding the free amine (0.45 g, 59% yield).

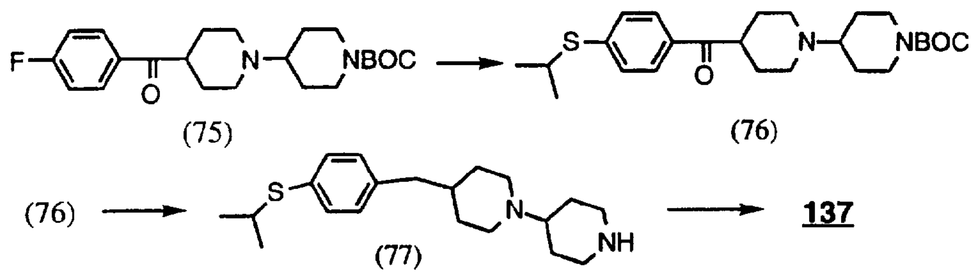
To a solution of the amine (23.6 mg, 53.3 μmol) in CH_2Cl_2 (0.53 ml) was added *o*-toluoyl chloride (8.3 μL, 64 μmol) and Et_3N (11 μL, 80 μmol). The reaction was stirred for 2 h at room temperature under N_2. The mixture was concentrated under reduced pressure and purified by

PTLC (10/90 CH_3OH/CH_2Cl_2), concentrated in the presence of 1N HCl/Et_2O, yielding <u>136</u> (15.8 mg, 50% over three steps).
LRMS calc'd: 560; found (M+H): 561.

Example 35



137



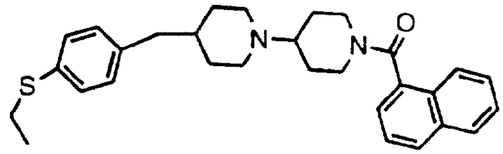
NaH (0.59 g, 14.6 mmol, 60% purity) was suspended in DMF (10 ml) followed by addition of 2-propanethiol (1 ml, 11.2 mmol) at 0°C under N_2. The reaction mixture was stirred at room temperature for 5 min. (75) (2.94 g, 7.5 mmol) in DMF (10 ml) was added dropwise. The reaction mixture was heated with stirring for 2 hrs. The reaction mixture was then diluted with 1N NaOH (40 ml) and extracted with Et_2O (3x 80 ml). The organic extract was dried with $NaHCO_3$. Removal of solvent and recrystallization with Et_2O afforded (76) (1.08 g, 32%).

(76) (1.08 g, 2.4 mmol) was dissolved in CH_3OH (10 ml) followed by addition of $NaBH_4$ (0.14 g, 3.6 mmol). The reaction mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with CH_2Cl_2 (200 ml) followed by washing with 1N NaOH (50 ml). The organic solution was dried with $NaHCO_3$ and concentrated to give solid residue which was then dissolved in CH_2Cl_2 (10 ml). To this solution was added Et_3SiH (1.5 ml) followed by TFA (3 ml). The reaction mixture was stirred at room temperature for 1hr. The reaction mixture was diluted with CH_2Cl_2 (100 ml), washed with 1N NaOH (100 ml), and dried with $NaHCO_3$. Removal of solvent afforded pure (77) (0.7 g, 88%).

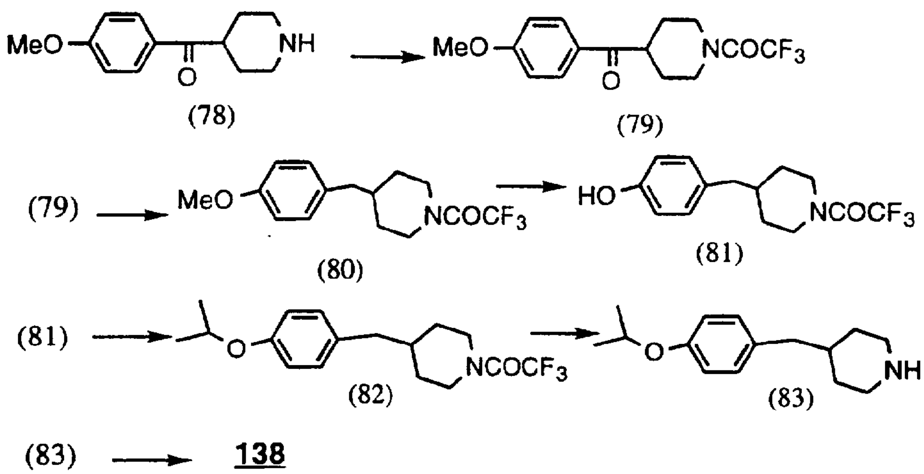
(77) (49 mg, 0.15 mmol) was dissolved in a solution of CH_2Cl_2 (3 ml) and Et_3N (0.3 ml) followed by addition of 1-naphthoyl chloride (0.5 ml). The reaction mixture was stirred for 30 min and separated by PTLC

to afford 137 (53 mg, 74%) as free base. HRMS: calc'd: (M+1): 487.2783; found 487.2798.

Example 36



138



(78) (1 g, 3.6 mmol) was dissolved in a solution of CH_2Cl_2 (20 ml) and Et_3N (1.5 ml) followed by addition of $(CF_3CO)_2O$ (0.82 ml, 5.7 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (150 ml), washed with 1N HCl (50 ml) followed by 1N NaOH (50 ml), and dried with $MgSO_4$. Removal of solvent afforded crude (79).

(79) was dissolved in CH_3OH (25 ml) followed by addition of $NaBH_4$ (0.2 g, 5.3 mmol). The reaction mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with CH_2Cl_2 (100 ml) followed by washing with 1N NaOH (50 ml). The organic solution was dried with $MgSO_4$ and concentrated to give a residue which was then dissolved in CH_2Cl_2 (30 ml). To this solution was added Et_3SiH (3 ml) followed by TFA (10 ml). The reaction mixture was stirred at room temperature for 4 hrs. The reaction mixture was diluted with CH_2Cl_2 (200 ml), washed with 1N NaOH (100 ml), and dried with $MgSO_4$. Removed solvent to afford crude (80).

(80) was dissolved in CH_2Cl_2 (5 ml) followed by addition of 1M BBr_3/CH_2Cl_2 (8.6 ml) at 0°C. The reaction mixture was stirred at 0°C for

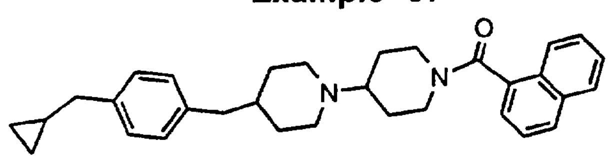
1 hr, diluted with CH_2Cl_2 (100 ml), washed with 10% $NaHCO_3$, and dried with $MgSO_4$. Removed solvent followed by column chromatography (20% EtOAc/hexane) to afford (81) (0.725 g, 58% from (78)).

(81) (0.35 g, 1.2 mmol), 2-propanol (0.084 g, 1.4 mmol) and PPh_3 (0.38 g, 1.4 mmol) were dissolved in THF (5 ml) under N_2. The reaction mixture was cooled to 0°C followed by addition of DEAD (0.27 ml, 1.mmol). The reaction mixture was stirred at room temperature overnight and separated by PTLC without workup to afford (82) (0.3 g, 75 %).

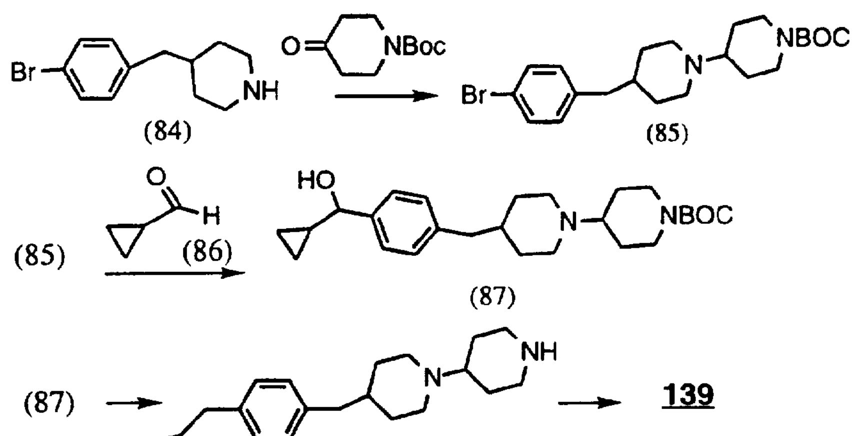
(82) (0.3 g, 0.9 mmol) was dissolved in a solution of CH_3OH/water (5:1) (10 ml) followed by addition of K_2CO_3 (0.5 g, 3.6 mmol). The reaction mixture was stirred at room temperature for 1h. Standard aqueous workup afforded (83) (0.203 g, 96%).

(83) was converted to **<u>138</u>** following the procedures described in Example 35. HRMS: calc'd: (M+1): 471.3012; found 471.3009.

Example 37



139



(84) (0.85 g, 3.4 mmol) and N-BOC-4-piperidone (1g, 5.0 mmol) were dissolved to 1,2-dichloroethane (50 ml) followed by addition of $Na(OAc)_3BH$ (2.2 g, 10.1 mmol). The reaction mixture was stirred at room temperature for two days. The reaction mixture was diluted with CH_2Cl_2 (200 ml), washed with 1N NaOH (100 ml) and dried with

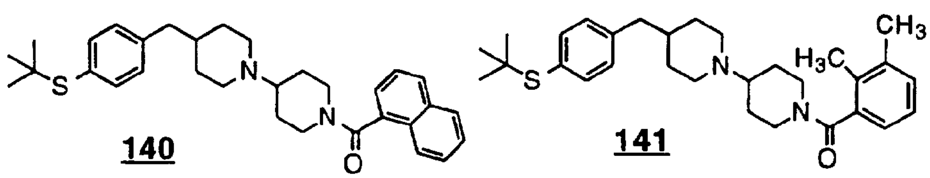
$NaHCO_3$. Column chromatography (5% CH_3OH/CH_2Cl_2) afforded (85) (1.27 g, 87%).

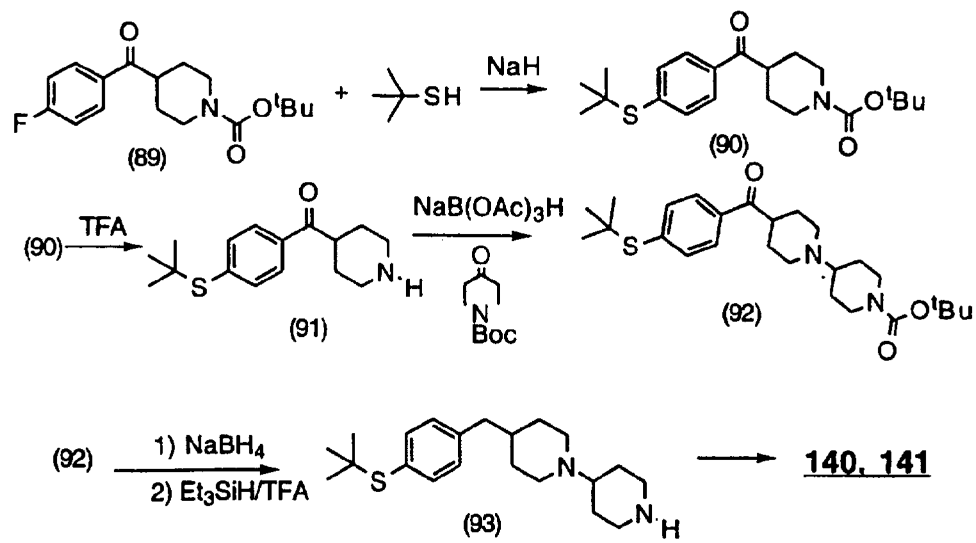
(85) (0.2 g, 0.46 mmol) was dissolved in THF (8 ml) under N_2 and cooled down to -78°C followed by addition of 2.5 M n-BuLi (0.3 ml, 0.73 mmol). The reaction mixture was stirred at -78°C for 45 min followed by addition of a solution of (86) (0.06 g, 0.83 mmol) in THF (1 ml). The reaction mixture was stirred at -78°C for 30 min, diluted with CH_2Cl_2 (100ml), washed with water (50 ml), and dried with $NaHCO_3$. The organic solution was concentrated and column chromatography (5% CH_3OH/CH_2Cl_2) afforded (87) (0.135 g, 69%).

To a mixture of (87) (0.135 g, 0.32 mmol) and Et_3SiH (1ml) was added 20% TFA/CH_2Cl_2 (5 ml). The reaction mixture was stirred at room temperature for 1h and concentrated to give (88) (0.09 g, 91%).

(88) was treated in a manner similar to that decribed in Example 35 to obtain <u>139</u>. HRMS: calc'd: (M+1): 467.3062; found 467.3066.

Examples 38A and 38B





To a suspension of 500 mg of NaH (60% in mineral oil) in 60 ml of DMF was added slowly 1.0 g of tert-butyl thiol. The mixture was stirred at room temperature for 30 min. To this mixture, 3.1 g (10 mmol) of ketone

(89) was added dropwise. The mixture was heated at 70°C overnight. After cooling down to room temperature, the mixture was quenched with 100 ml of water. The aqueous phase was extracted with 3X100 ml of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude (90) was purified by column chromatography on silica gel using 5% EtOAc-Hexanes (2.65 g, 69%).

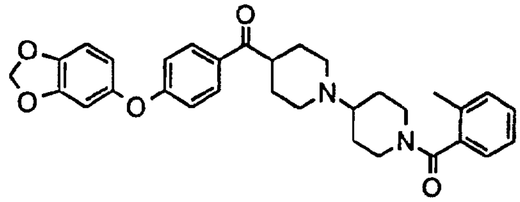
To a solution of 2.65 g of (90) in 40 ml of CH_2Cl_2 was added 10 ml of TFA. The mixture was stirred at room temperature for 2 hours and then was concentrated. The residue was taken up in 100 ml of CH_2Cl_2, washed with 10% NaOH. The organic layer was dried over Na_2SO_4, filtered and concentrated to give a crude (91) (1.8 g, 92%).

A mixture of (91) (1.8 g), N-Boc-4-piperidone (1.5 g, 1.1 eq.), $NaB(OAc)_3H$ (2.8 g, 2 eq.) and 0.5 ml HOAc in 40 ml of 1,2-dichloroethane was stirred at room temperature over night. The mixture was quenched with 10% NaOH, extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude (92) was purified by column chromotography on silica gel using 20% EtOH/EtOAc (2.7 g, 90.3%).

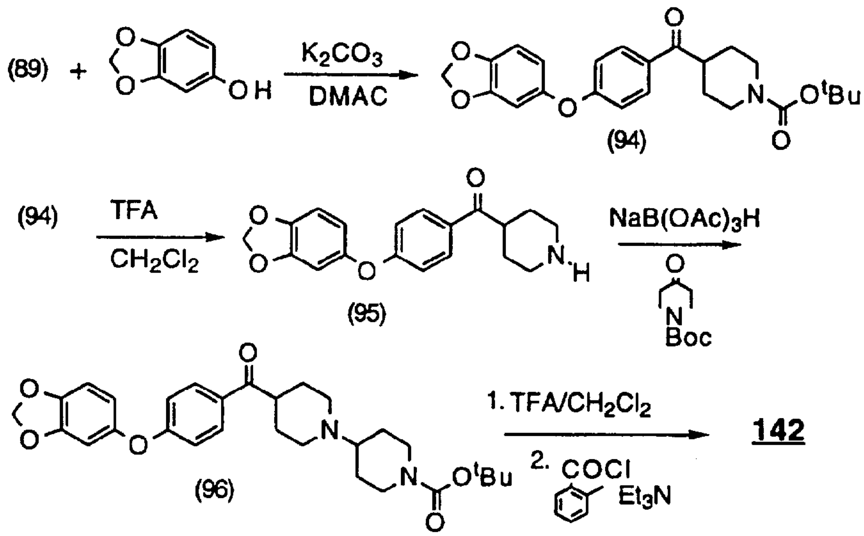
To a solution of (92) (2.5 g) in 100 ml of CH_3OH was added 500 mg (2 eq.) of $NaBH_4$. The mixture was stirred at room temperature for 1 hour and then was concentrated to dryness. The residue was taken up in 70 ml of 10% NaOH and extracted with 3X70 ml of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated (1.8 g crude). This crude was dissolved in 40 ml of CH_2Cl_2 and 1ml of Et_3SiH. To this mixture was added 20 ml of TFA and stirred at room temperature for 1 hour. The mixture was concentrated to dryness and the residue was washed with cold hexanes. The residue was taken up in 100 ml of CH_2Cl_2 and washed with 10% NaOH. The combined organic phases were dried over $MgSO_4$, filtered and concentrated to give a crude (93) (810 mg, 43%).

(93) and 1.3 ml (4 eq.) of Et_3N were dissolved in 40 ml of 1,2-dichloroethane and this solution was used for parallel synthesis to react with different acid chlorides. Typical yield of the coupling reaction is 80%. The Hcl salts were prepared by adding HCl•OEt_2 to the free base. **140**: LRMS calc'd: 500; found 501; **141**: LRMS calc'd: 478; found 479.

Example 39



142



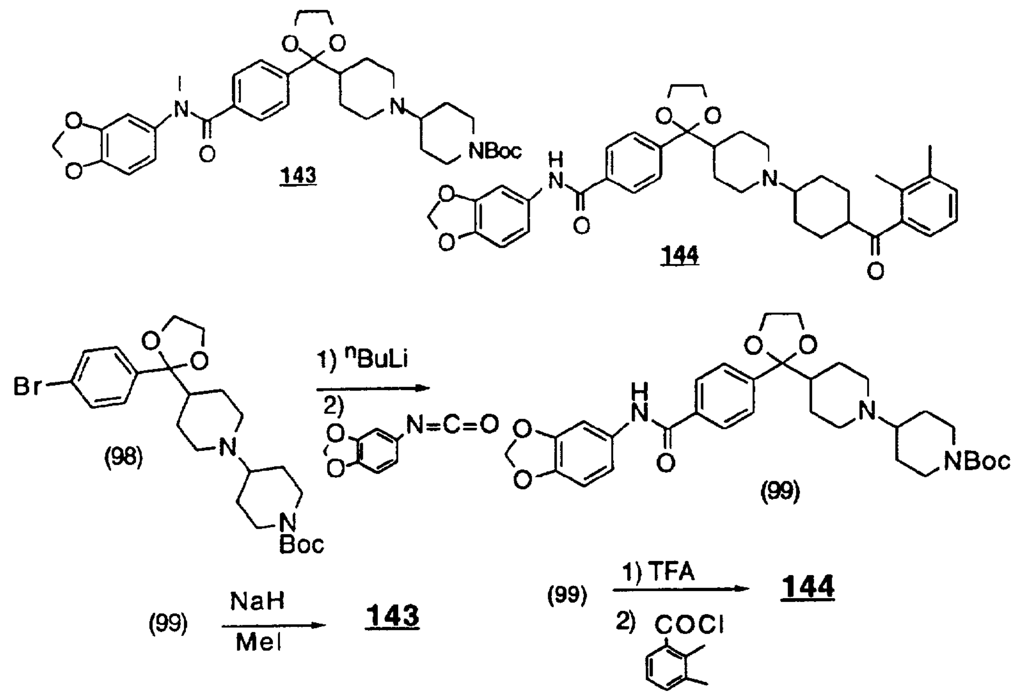
A mixture of (89) (7.9 g, 25.6 mmol), sesamol (1.1 g, 1 eq.) and K_2CO_3 (1.5 g) in 40 ml of dimethylacetamide was heated at 150°C over night. The mixture was allowed to cool to room temperature and then was quenched with 200 ml of water. The aqueous phase was extracted with 3X150 ml of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude (94) was purified by column chromatography on silica gel using 20% EtOAc-Hexanes (2.8 g, 26%).

To a solution of (94) (2.8 g) dissolved in 50 ml of CH_2Cl_2 was added 5 ml of TFA. The mixture was stirred at room temperature for 1 h and was then concentrated to dryness. The residue was taken up in 150 ml of CH_2Cl_2, washed with 100 ml of 10% NaOH. The aqueous layer was extracted with 3X100 ml of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated to give crude (95) as a solid (1.7 g, 79%).

The crude (95) (1.7 g, 5.2 mmol) was treated with N-BOC-4-piperidone, NaB(OAc)3H and acetic acid (1.3 g, 4 eq.) in a manner similar to that described in Example 38 to obtain crude (96) (2.3 g, 87%).

The BOC-group was removed to give a crude (97) (1.7 g, 93%), which was reacted with 2-toluoyl chloride as described in Example 14, Step 8, followed by purification by TLC on silica gel using 20% EtOH-EtOAc to obtain **142** (197 mg, 90%). The hydrochloride salt was prepared by adding HCl•Et2O to the free base. LRMS calc'd: 526; found: 527.

Examples 40A and 40B

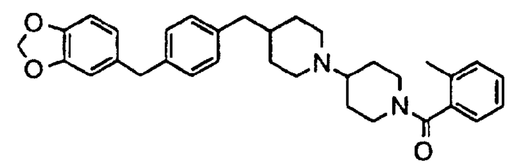


To a stirred solution of 500 mg of (98) in 10 ml of THF was added 0.6 ml of BuLi (2 M in hexane) at -78°C. The mixture was stirred at this temperature for 15 mins. and then a solution of 179 mg of the isocyanate in 15 ml of THF was added. The mixture was stirred at -78°C for 1 hour. The mixture was quenched with water, extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude (99) was purified by prep.TLC on silica gel using 25%EtOH-EtOAc (388 mg).

To a stirred solution of 328 mg of (99) in 50 ml of THF was added 41 mg (60% in mineral oil) NaH, followed by 85 mg of CH_3I. The mixture was stirred at room temperature for 1 hour and then was purified by prep. TLC on silica gel using 25%EtOH-EtOAc to obtain 141 mg of **143**. LRMS calc'd: 593; found: 594.

To 92 mg of (99) in 20 ml of CH_2Cl_2 was added 5 ml of TFA. The solution was stirred at RT for 1 hour, quenched with 10% NaOH, extracted with CH_2Cl_2. The organic layer was dried (K_2CO_3), filtered and concentrated (66 mg crude). This crude was dissolved in 20 ml of CH_2Cl_2, added 0.25 ml of Et_3N followed by 0.25 ml (1M in CH_2Cl_2) of 2,3-dimethylbenzoyl chloride. The mixture was stirred at RT for 1 hour and was purified by prep. TLC using 25%EtOH-EtOAc to obtain 81 mg **144**. LRMS calc'd: 611; found: 612.

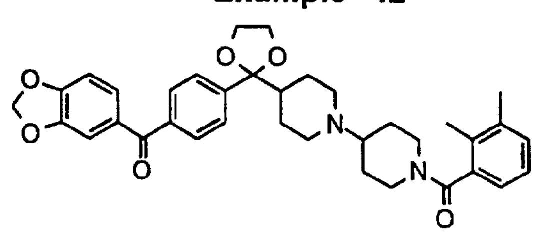
Example 41



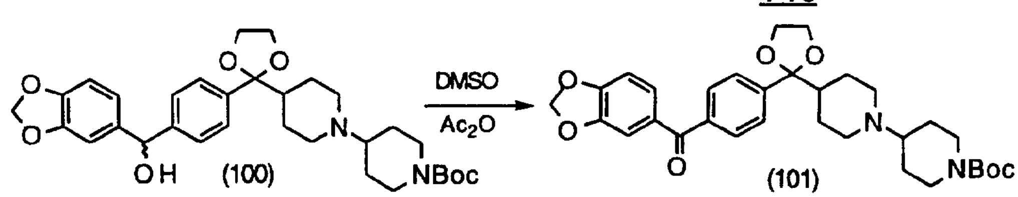
145

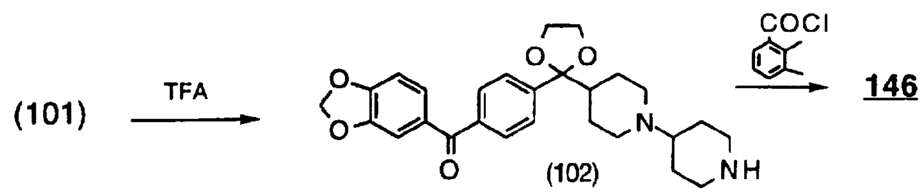
To a stirred solution of **83** (255 mg) in 50 ml of CH_3OH was added 186 mg of $NaBH_4$, the mixture was stirred at room temperature for 30 min. and was then quenched water. The mixture was extracted with EtOAc and the organic layer was dried over Na_2SO_4, filtered and concentrated to give a yellowish oil (286 mg). The crude was dissolved in 10 ml of CH_2Cl_2 and 2ml of Et_3SiH. To this mixture, 2ml of TFA was added and the mixture was stirred at room temperature for 5 hours. The mixture was neutralized with 3N NaOH, the organic layer was dried over Na_2SO_4, filtered and concentrated. The crude was purified by prep. TLC on silica gel using 25%EtOH-EtOAc (20 mg, 10%).
LRMS: calc'd: 510; found: 511.

Example 42



146

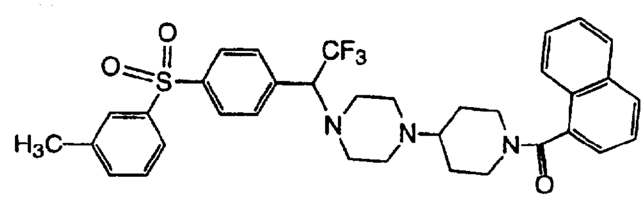




To a stirred solution of (100) in 10 ml of DMSO was added 10 ml of Ac_2O, the mixture was stirred at room temperature for 2 h, quenched with water and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude (101) was purified by prep. TLC on silica gel using 25%EtOH-EtOAc (110 mg). (101) was dissolved in 40 ml of CH_2Cl_2, and 5 ml of TFA was added. The mixture was stirred at room temperature for 30 min., concentrated to dryness. The residue was taken up in 100 ml of CH_2Cl_2 and was washed with 10% NaOH. The organic phase was dried (Na_2SO_4), filtered and concentrated to give a crude (102) (108 mg).

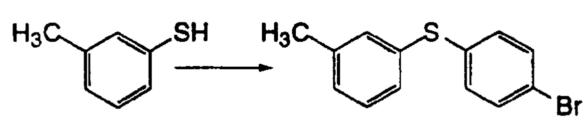
To a stirred solution of 28 mg of (102) and 0.1 ml of Et_3N in 3 ml of CH_2Cl_2 was added 0.25 ml of 2,3-dimethylbenzoyl chloride (1.0 M solution in CH_2Cl_2). The mixture was stirred at room temperature for 1.5 h. The crude was purified by prep. TLC on silica gel using 25%EtOH-EtOAc to obtain <u>146</u> (25 mg). LRMS calc'd: 596; found: 597.

Example 43



<u>147</u>

<u>Step1</u>:

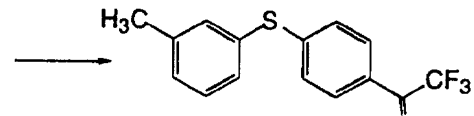


(103)

m-Thiocresol (5.0 g), 1-bromo-4-iodobenzene (10.5 g), CuI (7.7 g) and K_2CO_3 (20.0 g) in anhyd. DMF (100 ml) was heated at 130°C under N_2 overnight. The mixture was diluted with EtOAc and 10% NH_4OH/NH_4Cl and stirred, open to air, for 2 hours. The layers were separated, the organic phase was washed with the buffer solution 2x, followed by a water wash (3x). The organics were dried over sodium

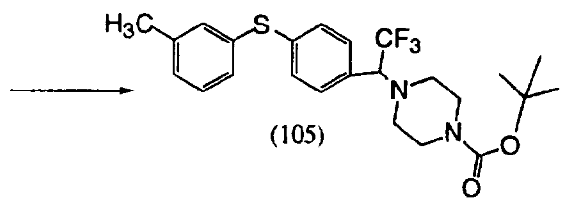
sulfate, filtered and concentrated to a dark brown oil. The crude was flash chromatographed (silica gel) eluted with hexane to give a pale yellow oil which solidified on standing under vacuum (10.9g of (103)).

Step 2:

(103)  (104)

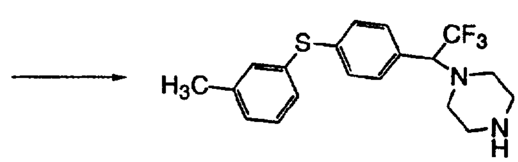
To a cold (-78°C) solution of (103) (2.0g) in anhyd. THF (50 ml) was slowly added n-BuLi (3.2 ml, 7.92 mmol) and the mixture was stirred at -78°C for 15 min. Ethyltriflouroacetate (1.53 g, neat) was added in one portion and this mixture was stirred at -78°C to room temp over 3 h. The mixture was poured into water, THF was removed in vacuo and the aqueous residue was extracted with EtOAc. The organics were washed with brine, dried over anhyd. Na_2SO_4 and concentrated to 1.97 g of a yellow oil, **2** (104)

Step 3:

(104)  (105)

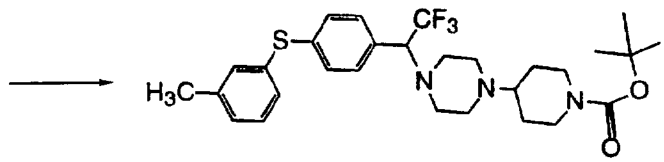
To a solution of crude (104) (1.9g) and t-butyl -1-piperazine-carboxylate (3.6 g) in dry dichloroethane (20 ml) was added titanium IV chloride (6.4 ml, 6.4 mmol) in portions. This was stirred at room temp. for 2 days. The reaction was cooled to 0°C and $NaBH_3CN$ (1.2 g) in CH_3OH (20 ml) was added. The mixture was stirred overnight at room temp, then filtered through a pad of celite. The layers were separated and the organic was washed with water and brine, then dried over Na_2SO_4, filtered and concentrated to a pale red viscous oil. The crude was purified by column chromatography eluted with hexane (neat) to 10% EtOAc/hexane to give 1.7g of viscous pale yellow oil, (105).

Step 4:

(105)  (106)

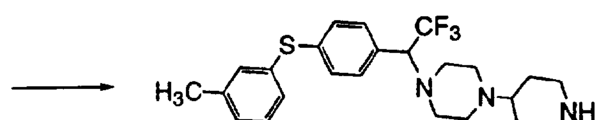
To a solution of (105) (1.72 g) in CH_2Cl_2 (25 ml) was added TFA (20 ml). he reaction was stirred for 1 hour, cooled to 0°C and neutralized with $NaHCO_3$. The aqueous phase was saturated with NaCl crystals and extracted with CH_2Cl_2. The organics were dried over Na_2SO_4, filtered and concentrated to 1.32g of viscous pale yellow oil, (106).

Step 5:

(106)  (107)

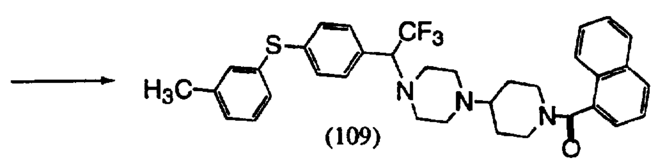
A solution of (106) (1.32g) and 1-t-butyloxycarbonyl-4-piperidone (858 mg) in dichloroethane (15 ml) was treated with $NaBH(OAc)_3$ (1.1 g) followed by HOAc (0.42 ml, 7.4 mmol). The mixture was stirred at room temp under N_2 for 4 days. The reaction was diluted with EtOAc, washed with 1N NaOH (2x), water, and brine. The organics were dried over Na_2SO_4, filtered and concentrated. The crude was purified by column chromatography eluted with 25% EtOAc/hexane to give 1.1g of viscous clear oil (107).

Step 6:

(107)  (108)

A solution of (107) (1.0 g) in anhyd. CH_2Cl_2 (10 ml) was treated with TFA (10 ml) and stirred at room temp, under N_2 for 1 hour. The mixture was then cooled to 0°C, neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organics were dried over Na_2SO_4, filtered and concentrated to 949 mg of pale yellow foam, (108).

Step 7:

(108)  (109)

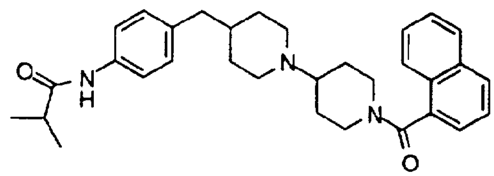
To a solution of (108) (100 g) in anhyd. CH_2Cl_2 (1.0 ml) containing Et_3N (38 µl, 0.27 mmol) was added 1-naphthoyl chloride (41 µl,0.27 mmol). This solution was stirred overnight at room temp. The

crude was purified by directly applying to a Preparative TLC plate (1x2000 micron) eluted with 5% Et_3N/EtOAc to give 86.4 mg of (109).

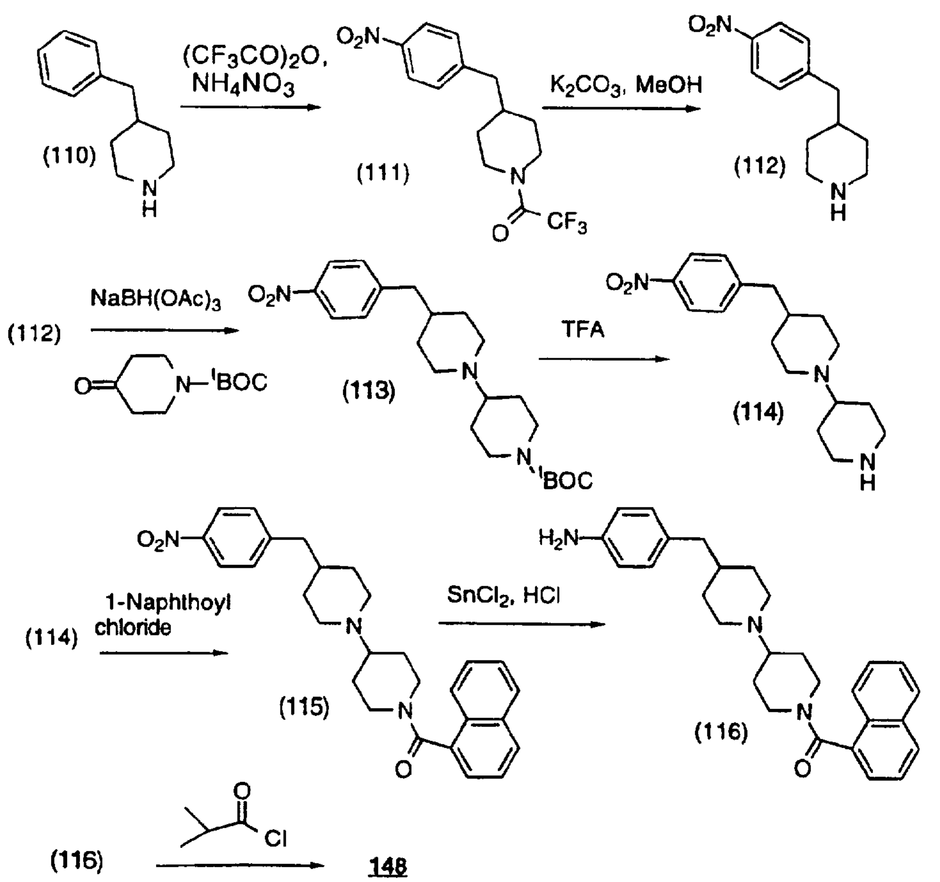
Step 8:

To a solution of (109) (63.3mg) in anhyd. CH_2Cl_2 (4.0 ml) was added 0.5M CH_3SO_2H solution in CH_2Cl_2 (1.2 ml. 0.6 mmol). After stirring for 0.5 h, 30% H_2O_2 (31μl, 0.6 mmol) was added and stirred overnight at room temp. The mixture was diluted with CH_2Cl_2, neutralized with saturated $NaHCO_3$. The layers were separated, dried over Na_2SO_4 and applied to a Preparative TLC plate (2000 micron) eluted with 5% Et_3N/EtOAc. Isolated 19.4 mg of 147. HRMS calc'd: 636.2508; found: 636.2509.

Example 44



148



To a stirred solution of (110) (9.3 g, 53.2 mmol) and NH_4NO_3 (4.4 g, 55.8 mmol) was added trifluroacetic anhydride (40 ml) at -15°C. The solvent was evaporated under vacum at rt. The resulting oil was then diluted with water and the compound was extracted with CH_2Cl_2 (2x50 ml). The combined organic layers were washed sequentially with dilute $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated and chromatographed to afford (111) (3.8 g, 43%) as colorless oil.

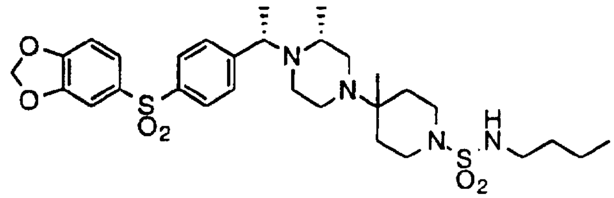
To a stirred solution of (111) (3.8 g, 12.0 mmol) in CH_3OH:H_2O (5:1) 100 ml was added K_2CO_3 (3.3 g, 24.0 mmol) and stirred for 3 h at rt. The reaction mixture was concentrated and poured into 2N NaOH and extracted with CH_2Cl_2 (2x50 ml). The combined layers were dried (Na_2SO_4), filtered, concentrated to yield (112) (1.79 g, 70%) as a colorless oil.

(112) was treated with N-BOC-4-piperidone, then extracted as described in Example 38 to yield (113) (0.700g, 20%) as a colorless oil.

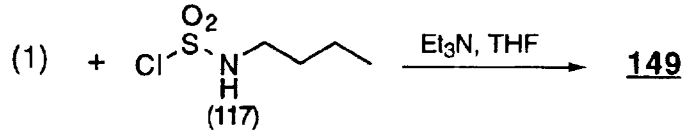
The BOC group on (113) was removed with TFA to obtain the amine (114), and (114) was reacted with 1-naphthoyl chloride as described in Example 14, step 8, to obtain (115) (0.448 g, 73%) as a colorless oil.

To a solution of (115) (0.170 g, 0.345 mmol) in CH_3OH (5 ml) was added $SnCl_2$ (0.262 g, 1.38 mmol) and concentrated HCl (1 ml) and the reaction was heated to reflux for 12 h. The reaction mixture was then cooled to rt and poured into 10% NaOH and extracted with CH_2Cl_2 (2x10 ml). The extracts were dried (Na_2SO_4), filtered, and concentrated to yield (116) (0.150 g, 100%).

To a solution of (116) (0.02 g, 0.047 mmol) in CH_2Cl_2 (1 ml) was added Et_3N (0.013 ml, 0.094 mmol) followed by isobutyryl chloride (0.010 ml, 0.07 mmol) and the mixture stirred at rt for 2 h. The reaction mixture was then poured into sat'd aq $NaHCO_3$ and extracted with CH_2Cl_2 (2x5 ml). The extracts were dried (Na_2SO_4), filtered , concentrated and chromatographed to yield **148** (0.014 g, 65%). LRMS: calc'd: 497; found ($M+H^+$): 498.

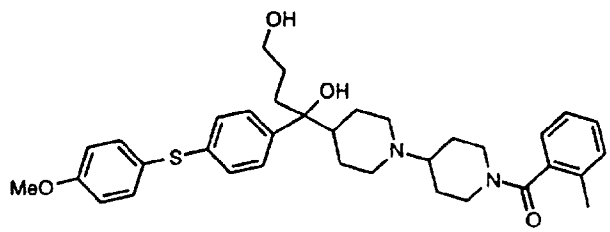


Example 45 **149**

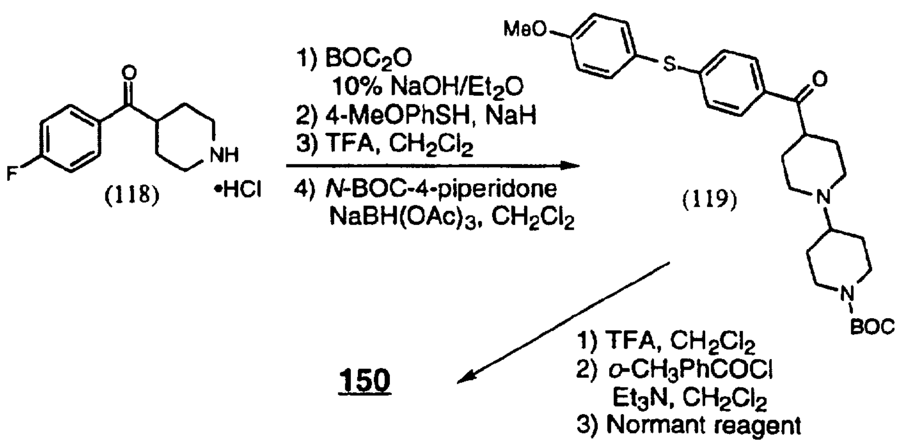


To a solution of (1) (20.0 mg, 0.042 mmol) in anhydrous THF (0.4 ml) at 0°C were successively added *n*-butyl sulfamoyl chloride (117) (literature prep.) (14.4 mg, 0.084 mmol) and Et_3N (11.8 µl, 0.084 mmol) and the resulting mixture was stirred 14 h at room temperature. After evaporation of the solvent, the residue was treated with saturated aquous $NaHCO_3$ solution (10 ml), extracted with CH_2Cl_2 (3 x 5 ml), dried over Na_2SO_4 and evaporated. Purification of the crude by preparative silica gel chromatography (eluent $CH_2Cl_2/CH_3OH/NH_3$ 96:4:1) provided 149 (17.3 mg, 66%) as an oil: MH+ = 621 (hydrochloride salt).

Example 46



150



To a stirred 0°C solution of (118) (50.0 g, 205 mmol) in a 1:1 solution of Et_2O/10% aq. NaOH (500 ml) was added a 2.5 M solution of di-*tert*-butyldicarbonate in Et_2O (100 ml, 246 mmol) over 30 min with vigorous stirring. After stirring at room temperature for 2 h, the mixture was extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting product (73.9 g) was used without further purification.

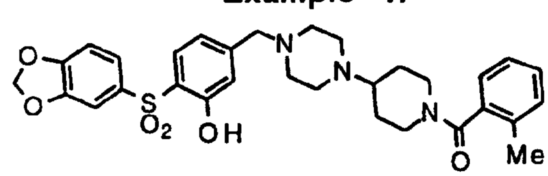
3,4-Methylenedioxythiophenol (19.1 g, 124 mmol) was added dropwise to a stirred 0°C suspension of NaH (5.46 g of a 60% dispersion, 136 mmol) in DMF (75 ml). After stirring 30 min at 0°C, (118) (31.8 g, 103 mmol) in DMF (75 ml) was added and the solution warmed to room temperature overnight. The reaction was quenched with water and extracted with EtOAc. The organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was recrystallized from EtOAc/hexanes, with the first two crops yielding 15.8 g pure sulfide (35% yield).

The sulfide was treated with TFA to obtain the free amine, then reacted with N-BOC-4-piperidone as described in Example 38 to obtain (119) (8.20 g, 69% yield).

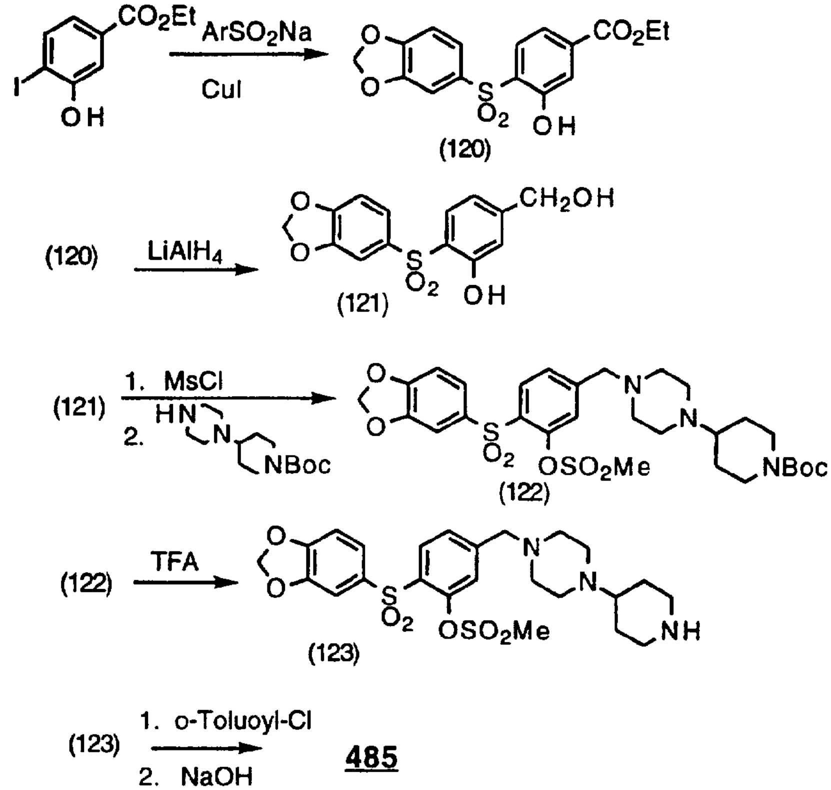
The BOC-group was removed and the resultant amine was reacted with 2-toluoyl chloride in a manner similar to that described in Example 14, Step 8. The mixture was concentrated under reduced pressure, yielding the aryl amide (0.65 g, 100% yield).

A solution of the aryl amide (0.21 g, 0.39 mmol) in THF (0.70 ml) was cooled to 0°C under N_2. A solution of Normant reagent (~ 0.5 M) in THF was added in 1 ml portions until the reaction was complete by TLC (10/90 CH_3OH/CH_2Cl_2). The reaction was quenched with NH_4Cl (sat), diluted with CH_2Cl_2, and 1 N NaOH was added. The aqueous layer was extracted with CH_2Cl_2, and the combined organics were dried over K_2CO_3, filtered, and concentrated to yield **150** (0.17 g, 71% yield). LRMS calc'd: 602; found (M+H): 603.

Example 47



485



4

Step 1: Ethyl 3-hydroxy-4-iodobenzoate (2.92 g), sodium 3,4-methylenedioxybenzenesulfinate (3.2 g), copper (I) iodide (2.8 g) and DMF (20 ml) were heated under N_2 for 20 h, added to 20% aqueous NaI (200 ml), extracted with EtOAc, dried and evaporated. The residue was flash-chromatographed on silica, eluting with hexanes-EtOAc, and pure fractions evaporated to give the product (120) as a solid (0.81 g), mp 133-135°C.

Step 2 (120) (0.40 g) in THF (5 ml) was added to a stirred, ice-cooled mixture of $LiAlH_4$ (0.08 g) and THF (10 ml). After 0.5 h, the mixture was treated with H_2O then 1N HCl, extracted with EtOAc, dried over $MgSO_4$ and evaporated to give (121), which was used in the next step.

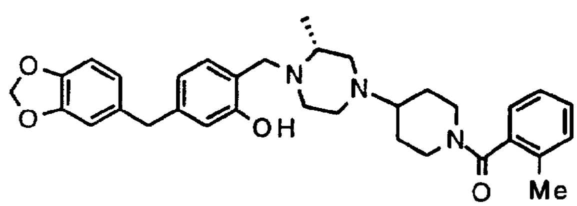
Step 3: (121) in CH_2Cl_2 (20 ml) and Et_3N (1.0 ml) was stirred with ice cooling and CH_3SO_2Cl (0.21 ml) added. After 0.5 h, the mixture was washed with 1N HCl, and then $NaHCO_3$ solution, dried and evaporated. This residue was stirred with diisopropylethylamine (0.3 ml) and the piperazine derivative (0.5 g) in DMF (3 ml) for 20 h at RT, worked up in water-EtOAc, dried, evaporated and

chromatographed on flash silica, eluting with 1 to 3% CH_3OH in CH_2Cl_2. Pure fractions were evaporated to give the product (122) as a white foam (0.60 g). Mass spectrum: MH+ = 638.

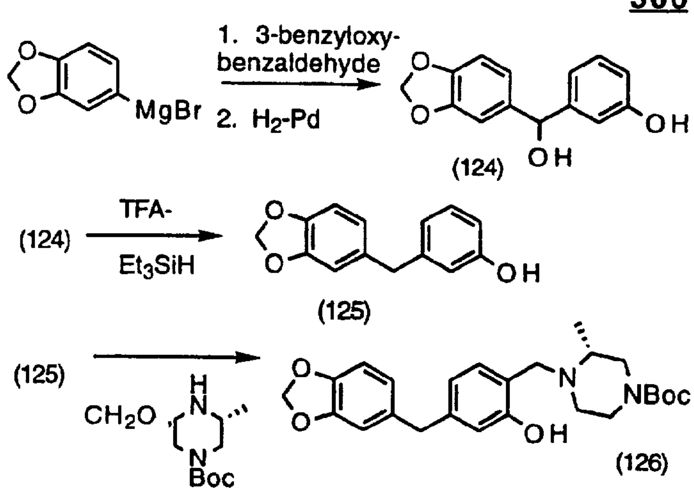
Step 4: (122) (0.43 g) was stirred for 45 min at RT in CH_2Cl_2 (2 ml) and 95% TFA (5 ml), evaproated, worked up in EtOAc - aq, $NaHCO_3$, dried, and evaporated to give (123) as a white foam (0.27 g). Mass spectrum: MH+ = 538.

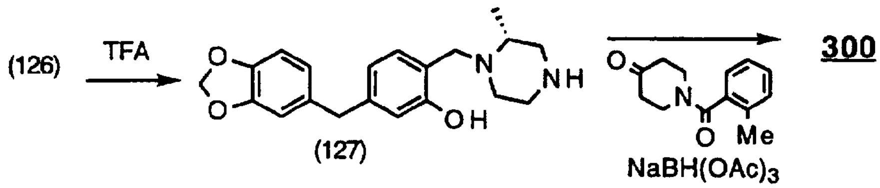
Step 5: (123) (0.07 g) and o-toluoyl chloride (0.06 g) were stirred for 45 min at RT in CH_2Cl_2 (5 ml) and saturated $NaHCO_3$ (5 ml). The mixture was extracted with CH_2Cl_2 and the organics were evaporated. The residue was sitrred for 0.5 h in a 5% solution of NaOH in 95% CH_3OH (4 ml), diluted with H_2O and CH_2Cl_2, and treted with stirring with small portions of solid CO_2 until the pH of the aq. phase was 7-8. The organic phase was dried and evaporated, and the residue dissolved in CH_2Cl_2 (2 ml) and added to Et_2O (15 ml) containing 4M HCl-dioxan (0.4 ml). The precipitate was centrifuged, the solid washed twice with Et_2O, and dried at RT in N_2 to give the hydrochloride of 485 as a white powder (0.051 g). Mass spectrum: MH+ = 607.

Example 48



300





Step 1: The Grignard reagent prepared by reacting 3,4-methylenedioxy bromobenzene (20 g) and Mg (3 g) in THF (60 ml) was cooled in ice and 3-benzyloxybenzaldehyde (16 g) in THF (60 ml) was added slowly. After 15 min, the mixture was added to a stirred mixture of ice and HCl (75 ml of 2N), extracted with Et_2O, washed with $NaHCO_3$ solution, dried and evaporated. The residue was extracted by stirring followed by decanting with hexanes (2 x 100 ml) and the residue was dried at high vacuum to a brown oil.

This material was shaken in H_2 (60 psi) at RT for 4 h in EtOAc (150 ml), HOAc (1.5 ml) and 20% palladium hydroxide on carbon (1.5 g). After filtration and evaporation, the residue was triturated with 1:1 Et_2O-hexanes (2 x 50 ml) and dried at RT to give (124) as a white solid (8.2 g). Mp 139-142°C.

Step 2: (124) (8.1 g) was stirred with Et_3SiH (20 ml) in CH_2Cl_2 (200 ml) and TFA (10 ml) was added dropwise. After 0.5 h. the solution was washed twice with H_2O and evaporated. The residue in CH_2Cl_2 (100 ml) was treated for 15 min. with 1M tetrabutylammonium fluoride in THF (50 ml), washed with 1N H_2SO_4, dried, evaporated and chromatographed on flash silica, eluting with 0 to 2% Et_2O in CH_2Cl2. Pure fractions on evaporation gave (125) as a thick oil (6.28 g). Mass spectrum: MH+ = 229.

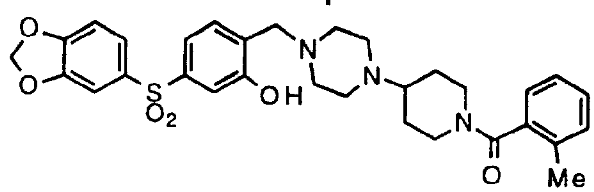
Step 3: A mixture of (125) (2.3 g), 4-t-butoxycarbonyl-2-(R)-methylpiperazine (2.4 g), ethanol (40 ml), 37% formalin (2.5 ml) and 4M HCl-dioxan (1.25 ml) was refluxed for 24 h, worked up in CH_2Cl_2: aq. $NaHCO_3$, dried, evaporated and the residue was chromatographed on flash silica, eluting with 5 to 30% Et_2O-hexanes. Pure fractions were evaporated to give (126) as a white foam (2.6 g). Mass spectrum: MH+ = 441.

Step 4: A solution of (126) (1.7 g) in CH_2Cl_2 (20 ml), H_2O (0.5 ml) and TFA (5 ml) was stirred at RT for 1 h., diluted with CH_2Cl_2 and H_2O, and treated with small portions of K_2CO_3 until the pH of the

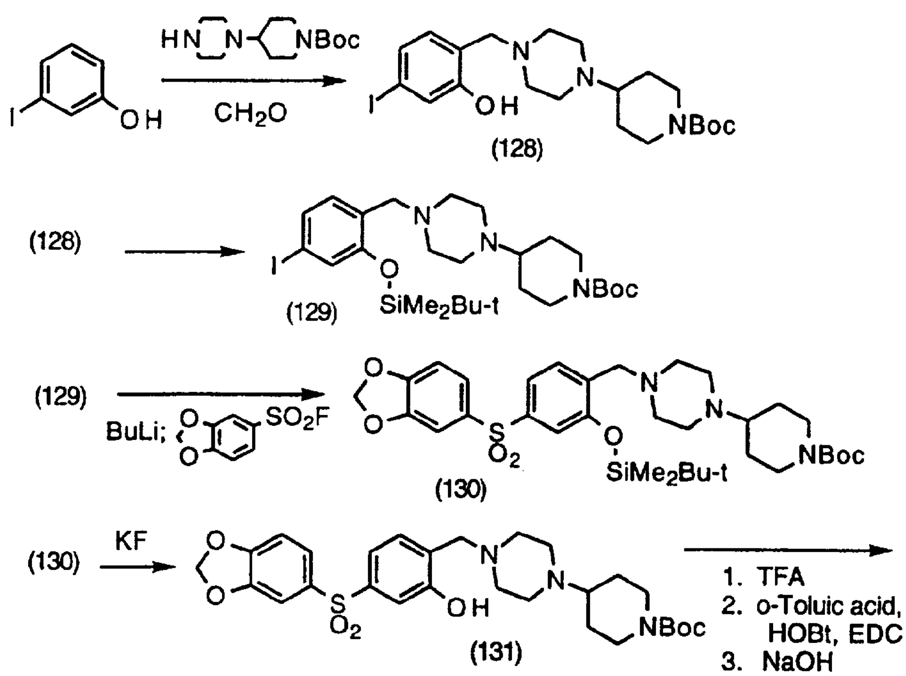
aqueous phase remained at 8-9. The organic phase was dried and evaporated to give (127) as a white foam (1.2 g). Mass spectrum: MH+ = 341.

Step 5: A mixture of (127) (1.12 g), 1-(o-toluoyl)-4-piperidinone (0.8 g), CH_2Cl_2 (25 ml) and $NaBH(OAc)_3$ (1.5 g) was stirred at RT for 20 h, washed with excess aq. $NaHCO_3$, dried and evaporated. The residue was dissolved in CH_3OH containing 4M HCl-dioxan (2 ml), evaporated, co-evaporated with CH_3OH (100 ml), and this residue dissolved in CH_3OH (1 ml) and CH_2Cl_2 (15 ml) and added to stirred Et_2O (100 ml) containing 4M HCl-dioxan (1 ml). The precipitate was filtered, washed with Et_2O and dried to give the hydrochloride of 300 as a white powder (1.76 g). Mass spectrum: MH+ = 542.

Example 49



210



210

Step 1: A mixture of 3-iodophenol (1.76 g), the piperazine (1.35 g), 37% formalin (1.25 ml) and ethanol (15 ml) was refluxed for 1 h, then addtiional formalin (0.75 ml) was added and heating continued for

10h. The reaction was cooled, worked up in CH_2Cl_2-H_2O, dried and evaporated. The major product was isolated by flash chromatography on silica, eluting with 0 to 1.5% CH_3OH in EtOAc. Evaporation of pure fractions gave a yellow foam, (128) (1.31 g). Mass spectrum: MH+ = 502.

Step 2: (128) (1.25 g) and t-butylchlorodimethylsilane (0.8 g) with Et_3N (0.8 ml) amd dimethylaminopyridine (0.03 g) was stirred in CH_2Cl_2 (30 ml) for 40h, evaporated, and chromatographed on flash silica in EtOAc to obtain the product (129) as a white foam (1.48 g). Mass spectrum: MH+ = 602.

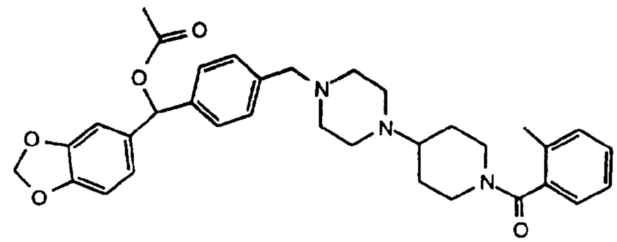
Step 3: A solution of (129) (1.42 g) in dry THF (25 ml) at -70°C was treated with n-BuLi in hexanes (2M; 1.4 ml). Immediately, a solution of 3,4-methylenedioxybenzenesulfonyl fluoride (0.65 g) in THF (1 ml) was added, and the mixure stirred to RT over 0.5h. The reaction was partitioned in H_2O - EtOAc, dried and evaporated, and the residue chromatographed on flash silica in hexanes-EtOAc. Pure fractions were evaporated to give the product (130) as a pale yellow foam (0.76 g). Mass spectrum: MH+ = 674.

Step 4: (130) (0.55 g) was stirred for 20 h in CH_3OH (15 ml) containing HOAc (0.1 g) and KF (1.0 g), partitoned in H_2O-CH_2Cl_2, dried and evaporated. Flash chromatography on silica with EtOAc gave the pure product (131) as a pale yellow foam (0.41 g). Mass spectrum: MH+ = 560.

Step 5: A mixture of (131) (0.37 g), CH_2Cl_2 (3 ml). H_2O (0.05 ml) and TFA (2 ml) was kept at RT for 2 h, evaporated, and partitioned in H_2O-CH_2Cl_2 with sufficient $NaHCO_3$ to maintain the aq. phase at pH 8-9. The CH_2Cl_2 extracts were dried and evaporated, and this residue in DMF (15 ml) stirred 20 h at RT with o-toluic acid (0.2 g), 1-hydroxybenzotriazole (0.15 g) and EDCI (0.4 g). The mixture was partitioned in EtOAc and aq. $NaHCO_3$, dried and evaporated. The major component was isolated by ptlc on silica plates with 3% CH_3OH-CH_2Cl_2 to give a white foam (0.38 g) which was mainly the N,O-di-toluoyl compound. 0.3 g of his material was stirred for 24 h at RT in CH_3OH (7 ml) and H_2O (0.8 ml) with NaOH (0.5 g). The solution was stirred with H_2O-CH_2Cl_2 and neutralised to pH 7-8 with

solid CO_2. The organic phase was dried and evaporated, and the hydrochloride of **210** precipitated as described in earlier examples, and dried at RT in vacuum to give a white solid (0.22 g). Mass spectrum: MH+ = 578.

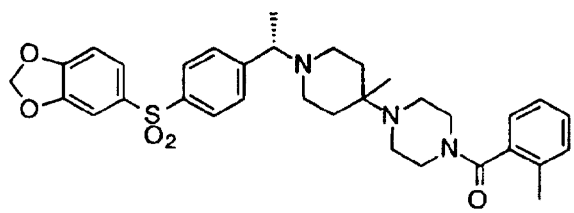
Example 50



520

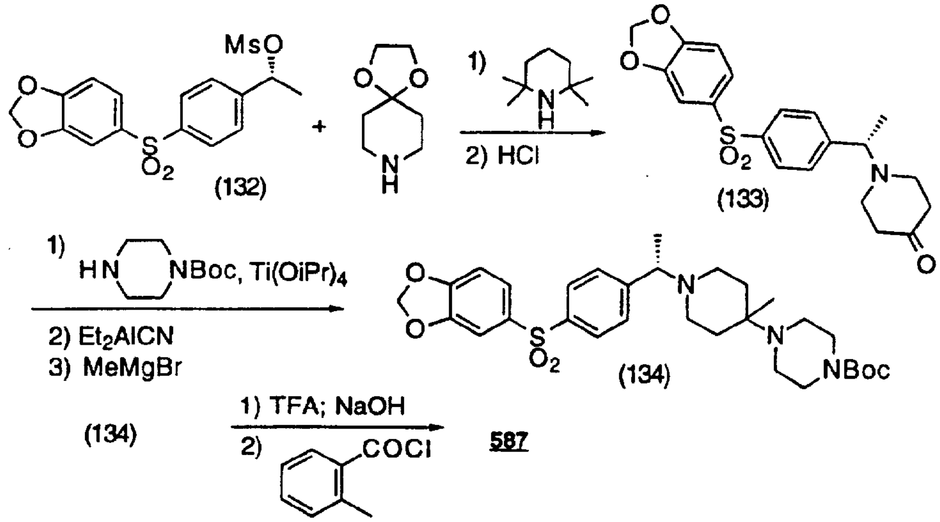
27 mg of **30** were taken up in 1.5 mL of glacial HOAc. The solution was stirred for 7 h at 40°C. Excess saturated $NaHCO_3$ solution was added, and the mixture was extracted with EtOAc. This was dried over Na_2SO_4, evaporated, and the residue purified by column chromatography in 10% CH_3OH/EtOAc, to give approx. 17 mg of **520** as an oil. MS (FAB): 598.4 (M+1), 538.5.

Example 51



. 2 HCl

587

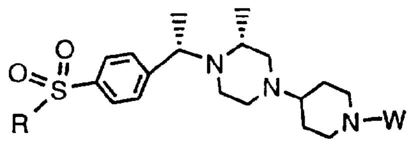


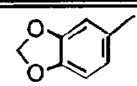
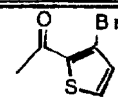
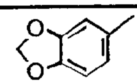
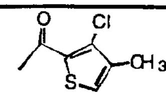
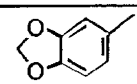
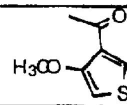
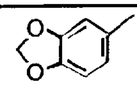
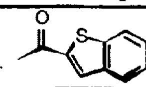
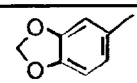
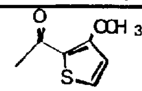
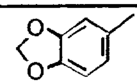
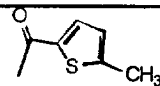
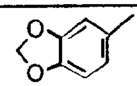
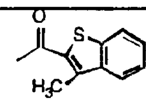
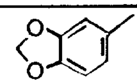
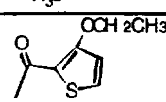
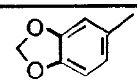
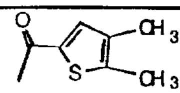
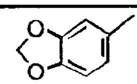
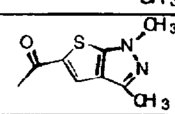
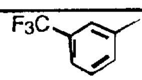
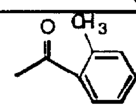
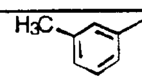
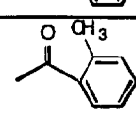
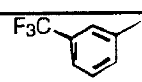
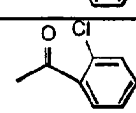
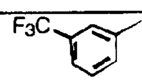
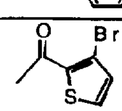
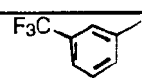
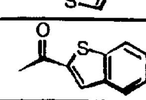
To a solution of (132) (2.31 g, 6.00 mmol) in anhydrous CH_3CN (30 ml) were successively added 4-piperidone ethylene ketal (0.77 ml, 6.00 mmol) and 2,2,6,6-tetramethyl piperidine (1.22 ml, 7.20 mmol), and the mixture was heated 14 h at 60°C. After evaporation of the solvent, the residue was taken up in saturated aqueous $NaHCO_3$ (100 ml), extracted with CH_2Cl_2 (3 x 50 ml), dried over Na_2SO_4, and evaporated. The oil thus obtained (2.89 g) was refluxed with 6 N HCl (40 ml) for 7 h then evaporated. Workup as above and purification by flash chromatography (SiO_2, $CH_2Cl_2/CH_3OH/NH_3$ 96:4:1) afforded (133) (1.26 g, 49%).

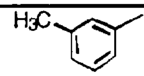
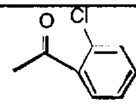
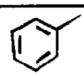
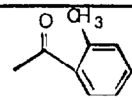
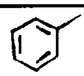
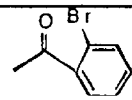
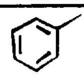
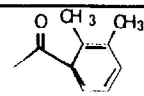
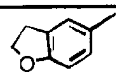
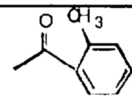
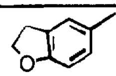
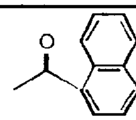
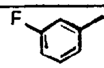
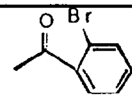
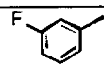
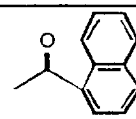
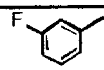
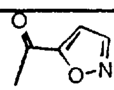
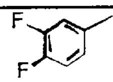
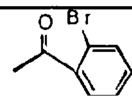
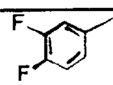
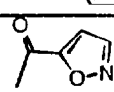
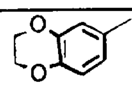
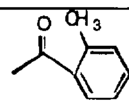
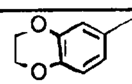
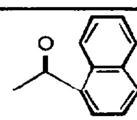
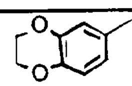
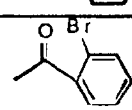
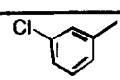
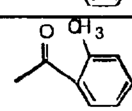
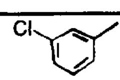
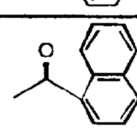
To a solution of (133) (470 mg, 1.21 mmol) and *N*-Boc piperazine (255 mg, 1.27 mmol) in anhydrous CH_2Cl_2 (1 ml) was added titanium (IV) isopropoxide (447 ml, 1.21 mmol), and the mixture was stirred 3 days at room temperature. The solution was diluted with CH_2Cl_2 (1 ml), Et_2AlCN 1 N in toluene (3.65 ml) was added at 0°C and the resulting mixture was allowed to warm to room temperature and stirred 2 h. Upon addition of Celite and water (100 ml), the final suspension was filtered over Celite, dried over Na_2SO_4 and evaporated. The crude thus obtained (655 mg, 93%) was dissolved in anhydrous THF (7 ml), treated at 0°C with CH_3MgBr 3 N in Et_2O (3.8 ml, 11.3 mmol) and the solution was allowed to warm to room temperature then heated 3 h at 55°C. After cooling, Celite (2 g) and CH_2Cl_2 (10 ml) were added and the suspension was slowly poured into ice. The resulting suspension was filtered over Celite and worked up as before to provide (134) (375 mg, 58%), after flash chromatography (SiO_2, eluent $CH_2Cl_2/CH_3OH/NH_3$ 80:20:1).

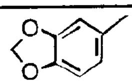
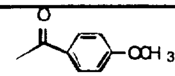
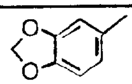
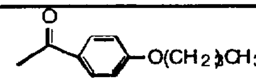
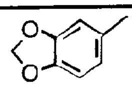
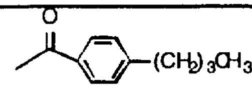
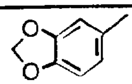
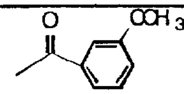
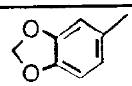
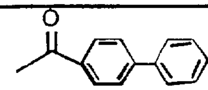
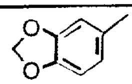
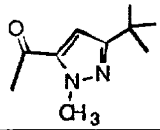
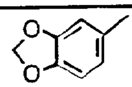
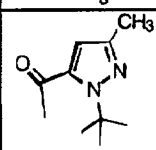
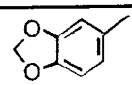
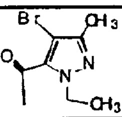
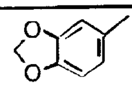
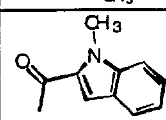
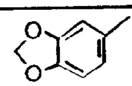
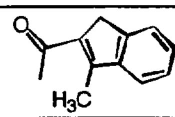
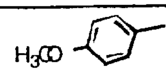
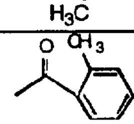
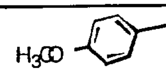
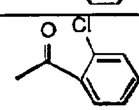
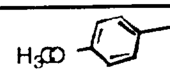
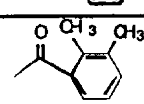
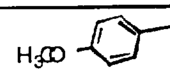
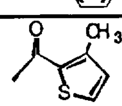
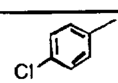
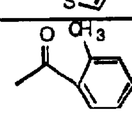
Removal of the Boc group with TFA gave, after basic workup with 1 N NaOH and extraction with CH_2Cl_2, 260 mg of intermediate. This (20 mg, 0.042 mmol) was subjected to *N*-acylation with *o*-toluoyl chloride to provide, after conversion to the hydrochlorid salt, <u>587</u> (15 mg) as a white solid: MH+ = 590.2.

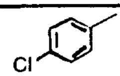
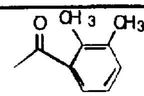
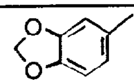
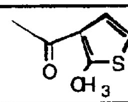
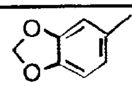
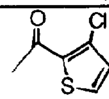
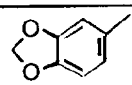
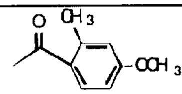
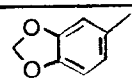
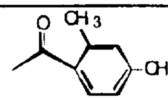
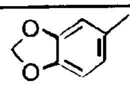
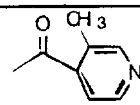
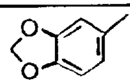
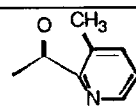
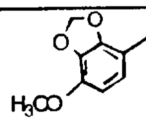
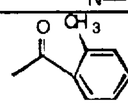
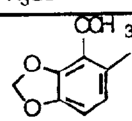
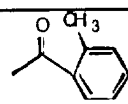
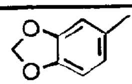
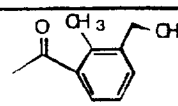
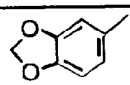
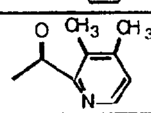
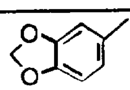
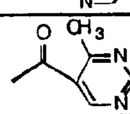
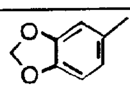
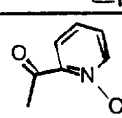
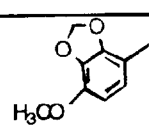
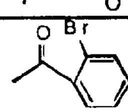
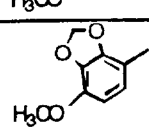
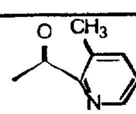
Using the appropriate starting materials in the procedures described above or modifications of those procedures well known to those skilled in the art, the compounds shown in the following tables are prepared.

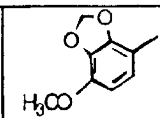
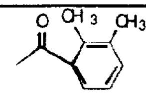
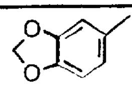
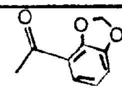
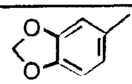
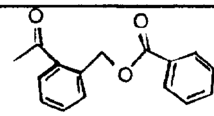
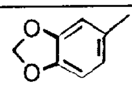
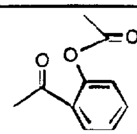
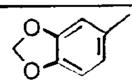
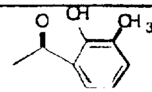


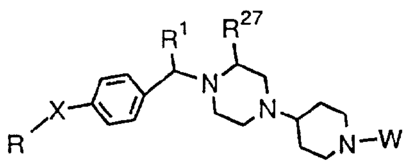
No.	R	W	Physical Data
151			m.p. = 198-206°C
152			m.p. = 186-192°C
153			(M-15) = 596
154			m.p. = 210-15°C
155			MH+ = 612
156			MH+ = 596
157			MH+ = 660
158			MH+ = 626
159			MH+ = 610
160			MH+ = 650
161			HRMS calc'd: 614.2664 found: 614.2664
162			HRMS calc'd: 560.2947 found: 560.2955
163			Mass spec. (FAB)M+1=635
164			Mass spec. (FAB)M+1=687
165			Mass spec. (FAB)M+1=656

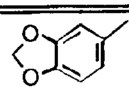
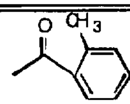
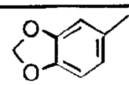
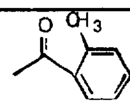
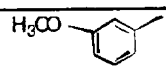
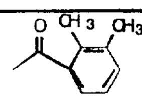
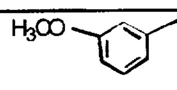
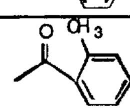
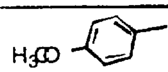
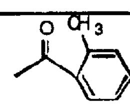
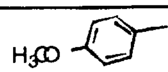
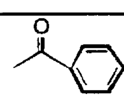
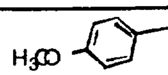
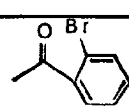
166			Mass spec. (FAB)M+1=580
167			HRMS calc'd: 560.2947 found: 560.2933
168			HRMS calc'd: 610.1738 found: 610.1739
169			HRMS calc'd: 546.2790 found: 546.2787
170			HRMS calc'd: 588.2896 found: 588.2897
171			HRMS calc'd: 624.2896 found: 624.2903
172			HRMS calc'd: 628.1645 found: 628.1646
173			HRMS calc'd: 600.2696 found: 600.2694
174			HRMS calc'd: 541.2285 found: 541.2289
175			HRMS calc'd: 646.1551 found: 646.1150
176			HRMS calc'd: 559.2191 found: 559.2202
177			HRMS calc'd: 604.2845 found: 604.2840
178			HRMS calc'd: 640.2845 found: 640.2840
179			HRMS calc'd: 668.1794 found: 668.1785
180			HRMS calc'd: 580.2401 found: 580.2401
181			HRMS calc'd: 616.2401 found: 616.2395

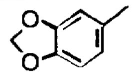
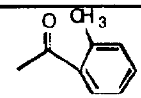
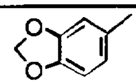
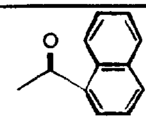
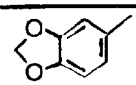
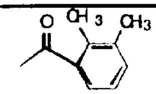
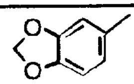
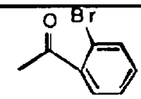
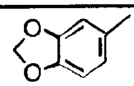
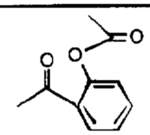
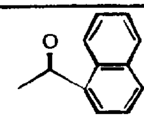
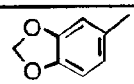
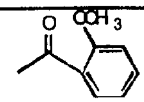
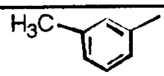
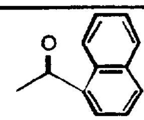
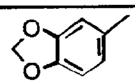
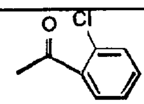
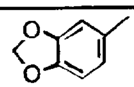
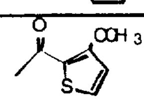
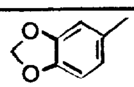
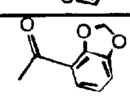
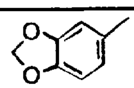
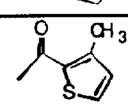
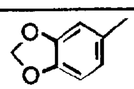
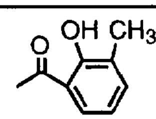
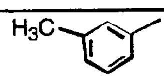
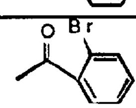
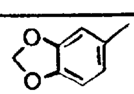
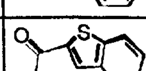
182			FAB(MH+) = 606
183			FAB(MH+) = 648
184			FAB(MH+) = 632
185			FAB(MH+) = 606
186			FAB(MH+) = 652
187			FAB(MH+) = 636
188			FAB(MH+) = 636
189			FAB(MH+) = 686
190			m.p. = 200-202^{o}C (dec)
191			m.p. = 201-203^{o}C (dec)
192			m.p. = 215-216^{o}C (dec)
193			m.p. = 210-201^{o}C (dec)
194			m.p. = 219-220^{o}C (dec)
195			FAB(MH+) = 582
196			m.p. = 204-206^{o}C (dec)

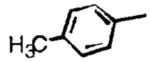
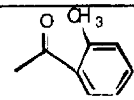
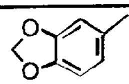
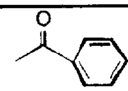
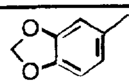
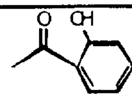
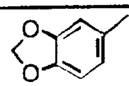
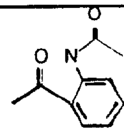
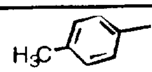
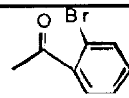
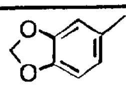
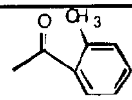
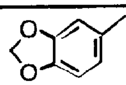
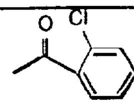
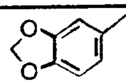
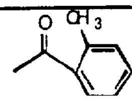
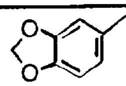
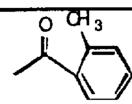
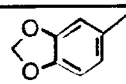
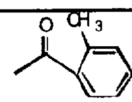
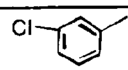
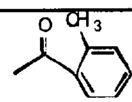
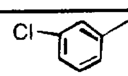
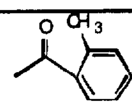
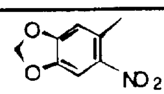
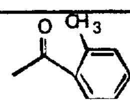
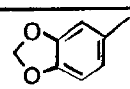
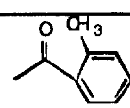
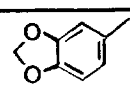
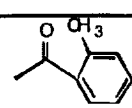
197			m.p. = 198-200^{0}C (dec)
198			MH+ = 596
199			MH+ = 610
200			MH+ = 620
201			MH+ = 606
202			MH+ = 541
203			MH+ = 591
204			MH+ = 620
205			MH+ = 620
206			MH+ = 620
207			MH+ = 605
208			MH+ = 592
209			MH+ = 520
211			MH+ = 684
212			MH+ = 621

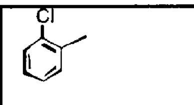
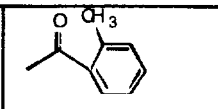
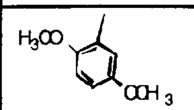
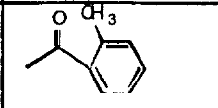
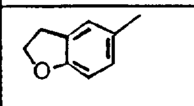
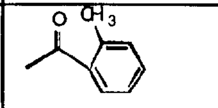
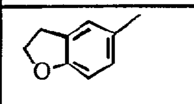
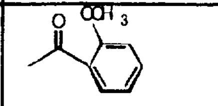
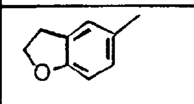
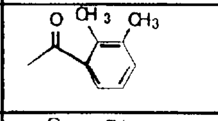
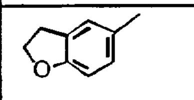
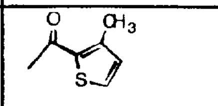
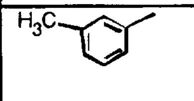
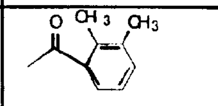
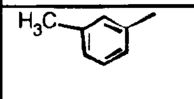
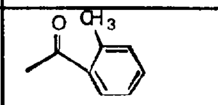
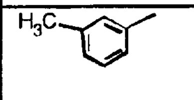
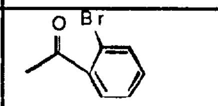
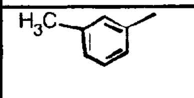
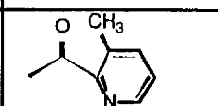
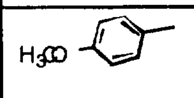
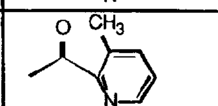
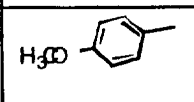
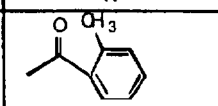
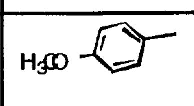
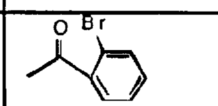
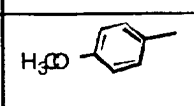
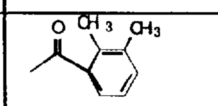
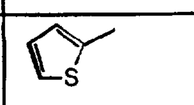
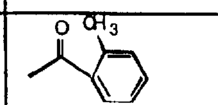
213			MH+ = 634
214			m.p.= decomp >225°C
215			m.p.= decomp 184°C
216			m.p.= decomp above 189°C
217			m.p.= 172-176°C

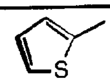
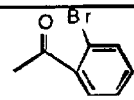
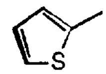
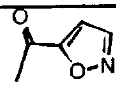
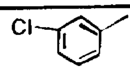
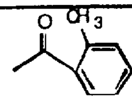
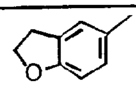
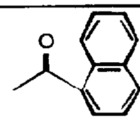
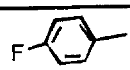
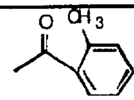
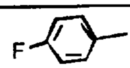
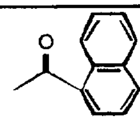
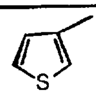
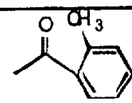
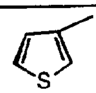
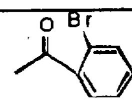
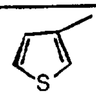
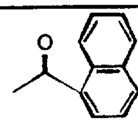
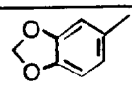
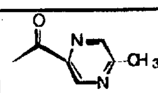
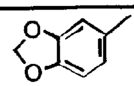
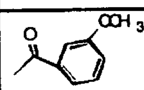
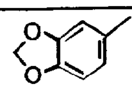
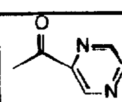
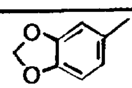
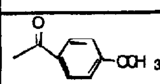
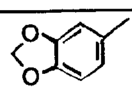
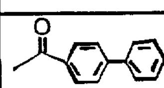
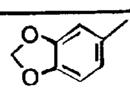
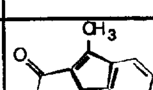


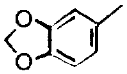
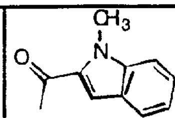
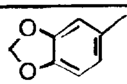
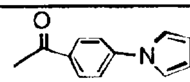
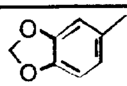
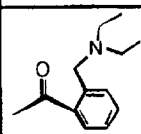
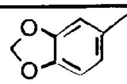
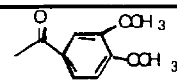
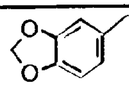
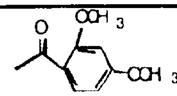
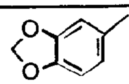
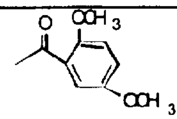
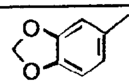
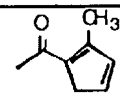
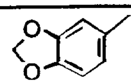
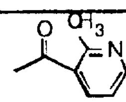
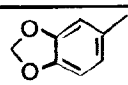
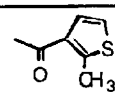
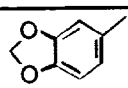
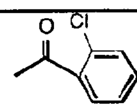
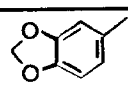
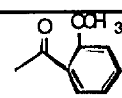
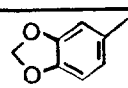
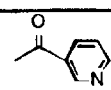
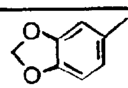
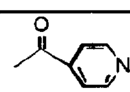
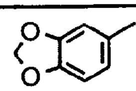
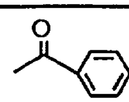
No.	R	W	R^1	R^{27}	X	Physical Data
218			H	H	-SO-	MS (electrospray): 546 (M+1), 487 (isomer A)
219			H	H	-SO-	MS (electrospray): 546 (M+1), 463 (isomer B)
220			H	H	$-SO_2-$	MS (FAB): 562 (M+1), 302
221			H	H	$-SO_2-$	MS (FAB): 548 (M+1), 461
222			H	H	$-SO_2-$	MS (electrospray): 548.2 (M+1), 465
223			H	H	$-SO_2-$	MS (electrospray): 534.2 (M+1), 472
224			H	H	$-SO_2-$	MS (electrospray): 613, 615 (M+1), 472

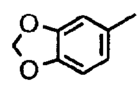
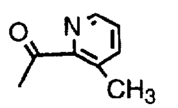
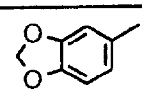
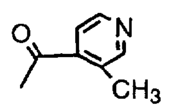
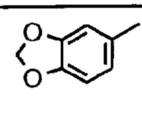
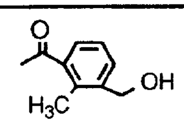
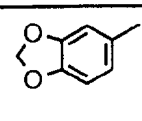
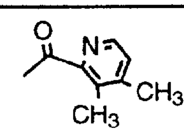
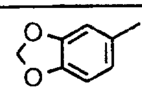
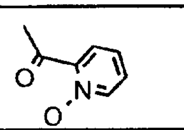
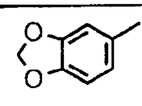
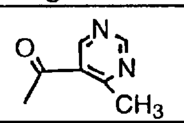
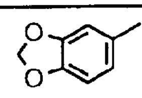
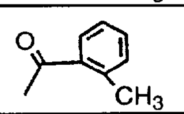
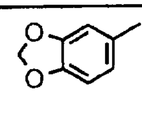
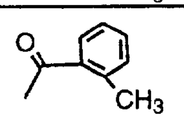
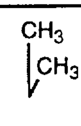
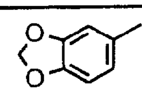
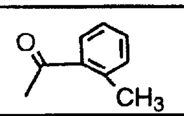
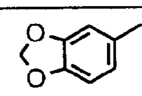
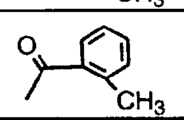
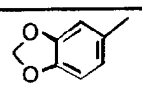
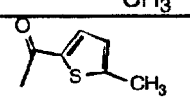
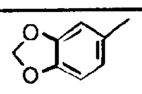
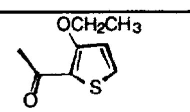
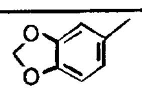
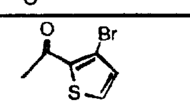
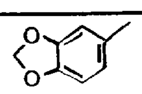
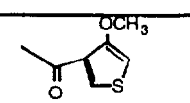
225			H	H	$-SO_2-$	m.p.= 230-246°C
226			H	H	$-SO_2-$	m.p.= 220°C (dec)
227			H	H	$-SO_2-$	m.p.= decomp above 245°C
228			H	H	$-SO_2-$	m.p.= 169-171°C
229			H	H	$-SO_2-$	m.p.= decomp above 235°C
230			H	H	$-SO_2-$	m.p.= decomp above 202°C
231			H	H	$-SO_2-$	m.p.= decomp above 208°C
232			H	H	$-SO_2-$	m.p.= decomp above 195°C
233			H	H	$-SO_2-$	m.p.= decomp above 235°C
234			H	H	$-SO_2-$	m.p.= decomp above 217°C
235			H	H	$-SO_2-$	m.p.= decomp above 185°C
236			H	H	$-SO_2-$	m.p.= decomp above 207°C
237			H	H	$-SO_2-$	m.p.= 164-166°C
238			H	H	$-SO_2-$	m.p.= decomp above 250°C
239			H	H	$-SO_2-$	m.p.= decomp above 239°C

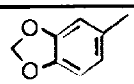
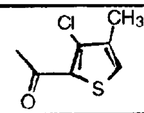
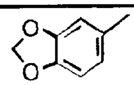
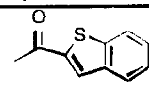
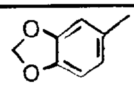
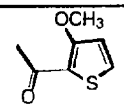
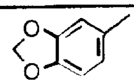
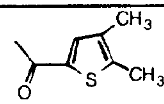
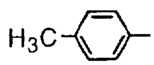
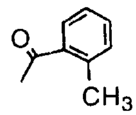
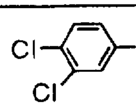
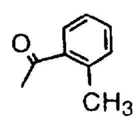
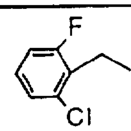
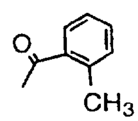
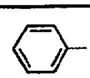
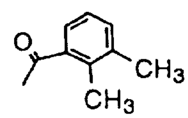
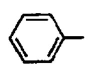
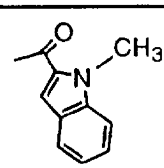
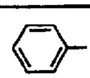
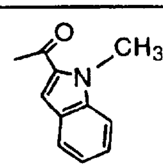
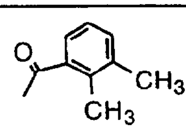
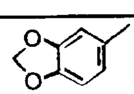
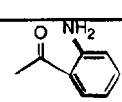
240			H	H	$-SO_2-$	m.p.= 204°C
241			H	H	$-SO_2-$	m.p.= decomp above 232°C
242			H	H	$-SO_2-$	m.p.= decomp above 205°C
243			H	H	$-SO_2-$	m.p.= decomp above 180°C
244			H	H	$-SO_2-$	m.p.= decomp above 200°C
245			CH_3	H	$-SO_2-$	MH+ = 576
246			CH_3	H	$-SO_2-$	MH+ = 596
247			H	CH_3	$-SO_2-$	m.p.= 174-177°C
248			CH_3	H	$-\overset{OH}{C}-$	MH+ = 542
249			H	H	$-\overset{O}{\overset{\parallel}{C}}-$	FAB(MH+) = 526
250			CH_3	CH_3	$-\overset{O}{\overset{\parallel}{C}}-$	HRMS calc'd: 544.2731 found: 544.2724
251			CH_3	CH_3	$-\underset{H}{\overset{OH}{C}}-$	Mass. Spec. (FAB)M+1 = 548
252			CH_3	CH_3	$-\underset{H}{\overset{OH}{C}}-$	Mass. Spec. (FAB)M+1 = 601
253			CH_3	H	$-CH_2-$	MH+ = 526
254			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 554.3383 found: 554.3366

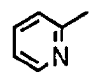
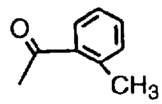
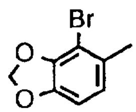
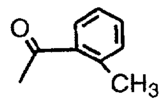
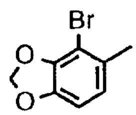
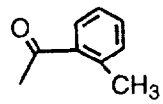
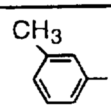
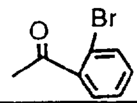
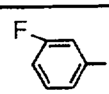
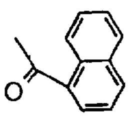
255			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 530.2938 found: 530.2943
256			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 556.3539 found: 556.3547
257			CH_3	CH_3	$-CH_2-$	Mass. Spec. (FAB)M+1 = 538
258			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 554.3383 found: 554.3366
259			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 552.3590 found: 552.3602
260			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 544.2998 found: 544.2987
261			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 524.3641 found: 524.3647
262			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 510.3484 found: 510.3476
263			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 574.2433 found: 574.2414
264			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 511.3437 found: 511.3448
265			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 527.3386 found: 527.3386
266			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 526.3434 found: 526.3442
267			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 590.2382 found: 590.2391
268			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 540.3590 found: 540.3611
269			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 502.2892 found: 502.2898

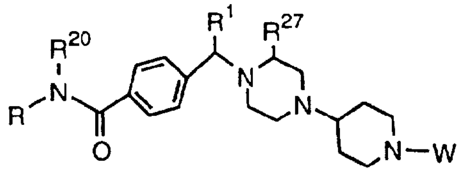
270			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 566.1841 found: 566.1839
271			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 479.2481 found: 479.2477
272			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 530.2938 found: 530.2954
273			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 574.3434 found: 574.3436
274			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 514.3234 found: 514.3233
275			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 550.3234 found: 550.3218
276			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 502.2892 found: 502.2893
277			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 479.2481 found: 479.2469
278			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 538.2892 found: 538.2884
279			CH_3	CH_3	$-CH_2-$	FAB(MH+) = 542
280			CH_3	CH_3	$-CH_2-$	FAB(MH+) = 556
281			CH_3	CH_3	$-CH_2-$	FAB(MH+) = 528
282			CH_3	CH_3	$-CH_2-$	FAB(MH+) = 556
283			CH_3	CH_3	$-CH_2-$	FAB(MH+) = 602
284			CH_3	CH_3	$-CH_2-$	FAB(MH+) = 578

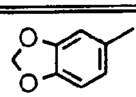
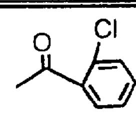
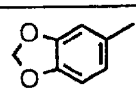
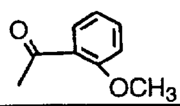
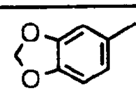
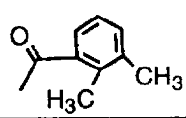
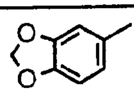
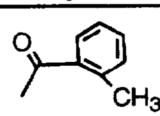
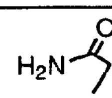
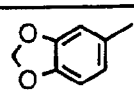
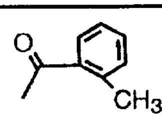
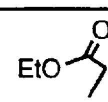
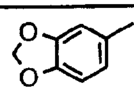
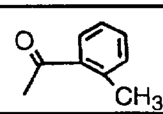
285			CH_3	CH_3	$-CH_2-$	FAB(MH+) = 579
286			CH_3	CH_3	$-CH_2-$	FAB(MH+) = 591
287			CH_3	CH_3	$-CH_2-$	FAB(MH+) = 611
288			CH_3	CH_3	$-CH_2-$	m.p.= 215-216^{o}C (dec)
289			CH_3	CH_3	$-CH_2-$	m.p.= 178-179^{o}C (dec)
290			CH_3	CH_3	$-CH_2-$	m.p.= 209-211^{o}C (dec)
291			CH_3	CH_3	$-CH_2-$	MH+ = 530
292			CH_3	CH_3	$-CH_2-$	MH+ = 541
293			CH_3	CH_3	$-CH_2-$	MH+ = 546
294			CH_3	CH_3	$-CH_2-$	MH+ = 561
295			CH_3	CH_3	$-CH_2-$	MH+ = 556
296			CH_3	CH_3	$-CH_2-$	MH+ = 527
297			CH_3	CH_3	$-CH_2-$	MH+ = 527
298			CH_3	CH_3	$-CH_2-$	MH+ = 526

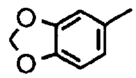
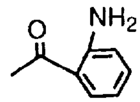
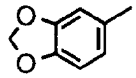
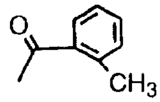
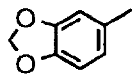
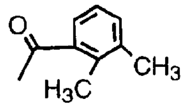
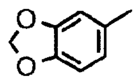
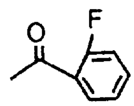
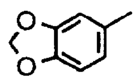
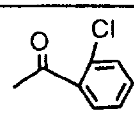
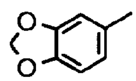
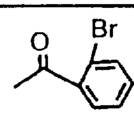
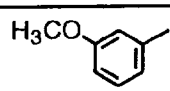
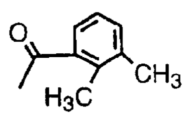
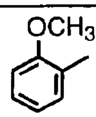
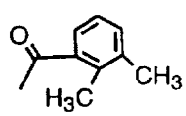
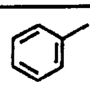
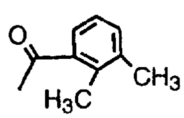
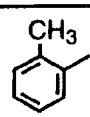
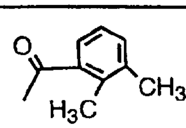
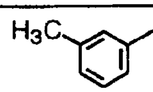
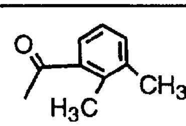
299			CH_3	CH_3	$-CH_2-$	MH+ = 541
301			CH_3	CH_3	$-CH_2-$	MH+ = 541
303			CH_3	CH_3	$-CH_2-$	MH+ = 570
304			CH_3	CH_3	$-CH_2-$	MH+ = 555
305			CH_3	CH_3	$-CH_2-$	MH+ = 543
306			CH_3	CH_3	$-CH_2-$	MH+ = 542
307			H	H	$-CH_2-$	m.p.= 216-223°C
308			H		$-CH_2-$	m.p.= decomp. above 145°C
309			H	CH_3	$-CH_2-$	m.p.= decomp. above110°C
309 A			H	CH_3	$-CH_2-$	m.p.= 228°C (dec)
494			CH_3	CH_3	$-CH_2-$	FAB(MH+) = 546
495			CH_3	CH_3	$-CH_2-$	FAB(MH+) = 576
496			CH_3	CH_3	$-CH_2-$	m.p. = 195-201 °C
497			CH_3	CH_3	$-CH_2-$	m.p. = 202-204°C

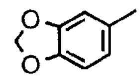
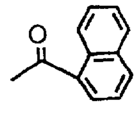
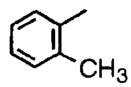
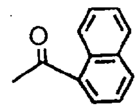
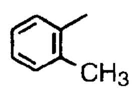
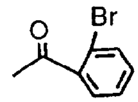
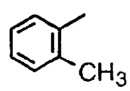
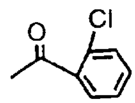
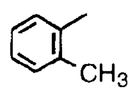
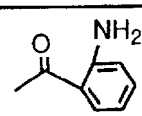
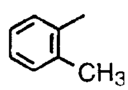
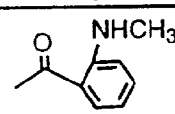
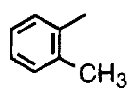
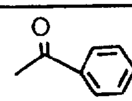
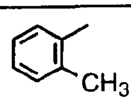
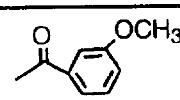
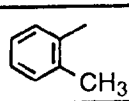
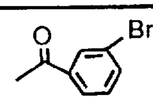
498			CH_3	CH_3	$-CH_2-$	m.p. = 202-204°C
499			CH_3	CH_3	$-CH_2-$	m.p. = 228-232°C
500			CH_3	CH_3	$-CH_2-$	MH+ = 562
501			CH_3	CH_3	$-CH_2-$	MH+ = 560
521			H	CH_3	-O-	m.p. = 197-199°C
522			H	CH_3	-O-	m.p. = 175-177°C
523			H	CH_3	-O-	m.p. = 195-197°C
524			H	CH_3	-O-	m.p. = 60-62°C
525			H	CH_3	-O-	m.p. = 196-200°C (isomer A)
526			H	CH_3	-O-	FAB(MH+) = 523 (isomer B)
527	H_3CO-		H	H	$-\overset{O}{\overset{\|}{C}}-$	HRMS (FAB) calc'd (MH^+): 450.2757 Found: 450.2752 m.p. = 245-260°C
559			H	H	$-SO_2-$	m.p.= decomp above 115°C

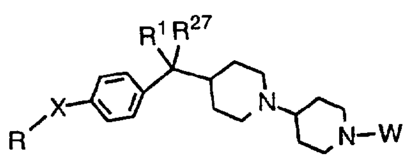
560			CH_3	CH_3	$-\overset{OH}{\underset{H}{C}}-$	m.p.= 161-166°C
561			CH_3	CH_3	$-\overset{OH}{\underset{H}{C}}-$	Mass. Spec. (FAB)M+1 = 635
562			CH_3	CH_3	$-CH_2-$	HRMS calc'd: 618.2331 found: 618.2316
592			$-CF_3$	H	$-SO_2-$	HRMS calc'd: 664.1456 found: 664.1452
593			CH_3	CH_3	$-\overset{OH}{\underset{H}{C}}-$	HRMS calc'd: 566.3183 found: 566.3180

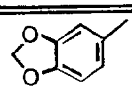
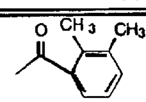
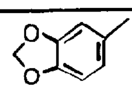
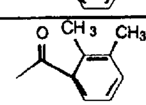
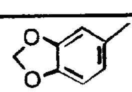
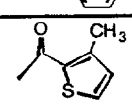


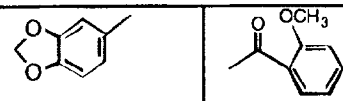
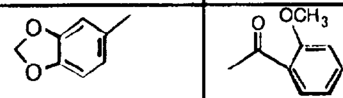
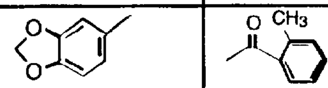
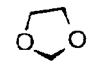
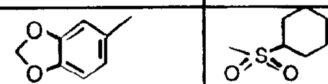
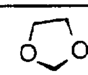
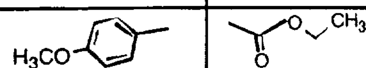
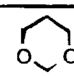
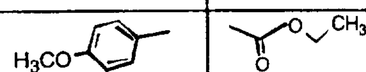
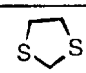
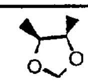
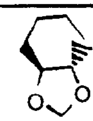
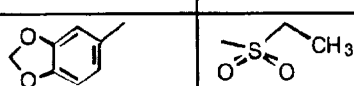
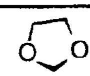
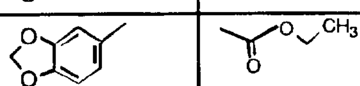
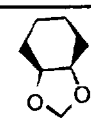
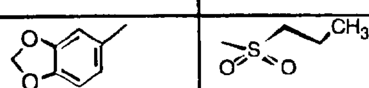
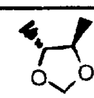
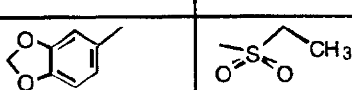
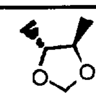
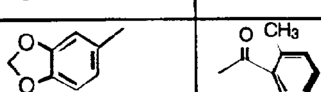
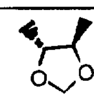
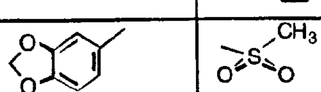
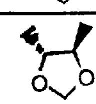
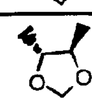
No.	R	W	R^1	R^{27}	R^{20}	Physical Data
310			CH_3	CH_3	$-CH_3$	MH+ = 603
311			CH_3	CH_3	$-CH_3$	MH+ = 599
312			CH_3	CH_3	$-CH_3$	MH+ = 597
313			CH_3	CH_3		MH+ = 626
314			CH_3	CH_3		MH+ = 655
315			CH_3	CH_3	n-Pr	MH+ = 611

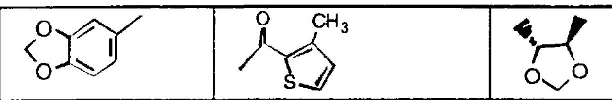
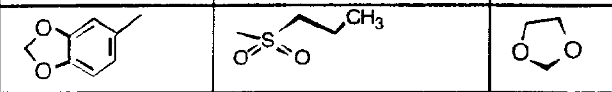
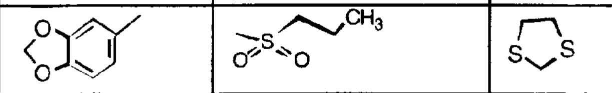
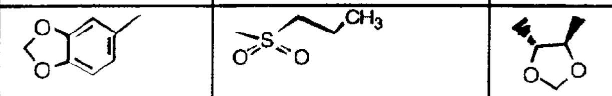
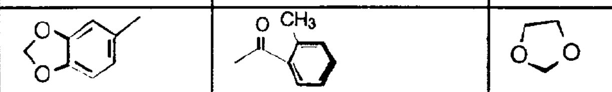
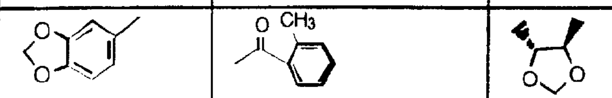
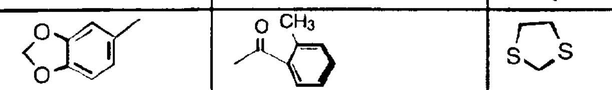
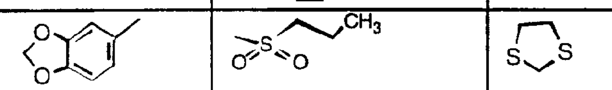
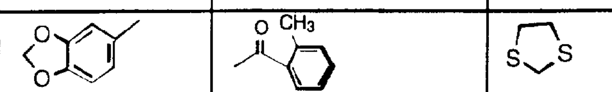
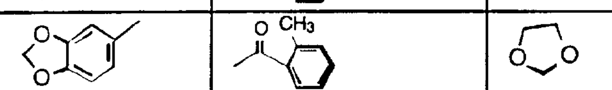
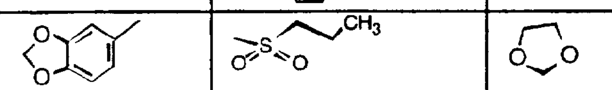
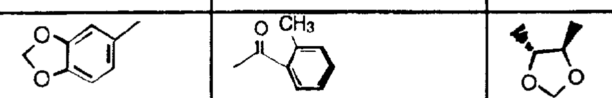
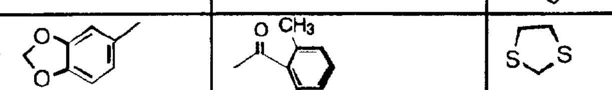
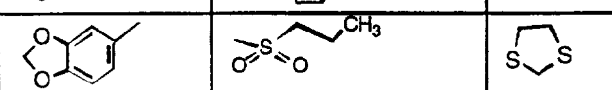
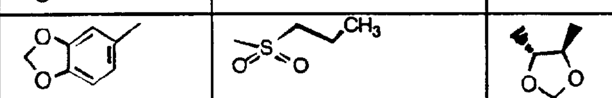
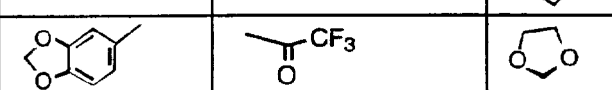
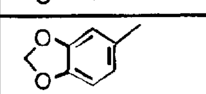
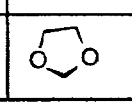
316			CH_3 (hashed)	CH_3 (hashed)	$-CH_3$	MH+ = 584
317			H	H	$-CH_3$	HRMS calc'd: 555.2971 found: 555.2983 m.p.=235-240°C
318			H	H	$-CH_3$	HRMS calc'd: 569.3128 found: 569.3132 m.p.=170-175°C
319			H	H	$-CH_3$	HRMS calc'd: 559.2721 found: 559.2732 m.p.=192-198°C
320			H	H	$-CH_3$	HRMS calc'd: 575.2425 found: 575.2418 m.p.=205-210°C
321			H	H	$-CH_3$	HRMS calc'd: 619.20 found: 619.1911 m.p.=170-180°C
322			H	H	$-CH_3$	HRMS calc'd: 555.3355 found: 555.3355 m.p.=175-185°C
323			H	H	$-CH_3$	HRMS calc'd: 555.3335 found: 555.3330 m.p.=180-190°C
324			H	H	$-CH_3$	HRMS calc'd: 525.3230 found: 525.3224 m.p.=205-210°C
325			H	H	$-CH_3$	HRMS calc'd: 539.3386 found: 539.3397 m.p.=228-237°C
326			H	H	$-CH_3$	HRMS calc'd: 539.3386 found: 539.3396 m.p.=234-239°C

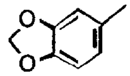
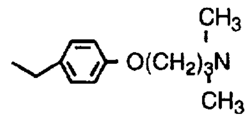
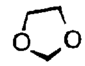
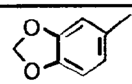
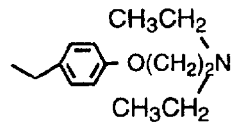
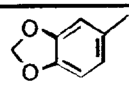
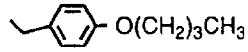
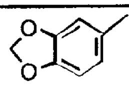
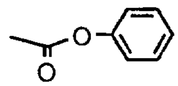
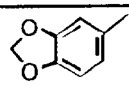
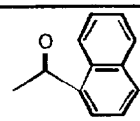
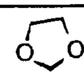
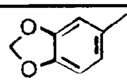
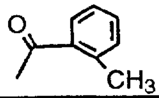
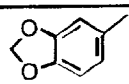
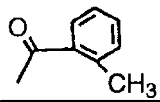
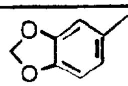
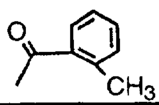
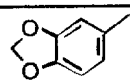
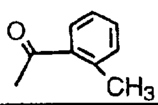
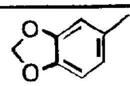
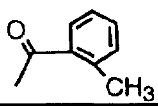
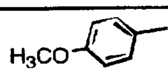
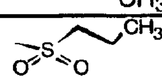
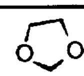
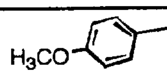
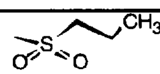
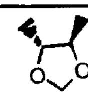
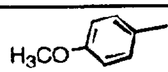
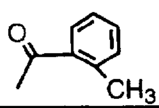
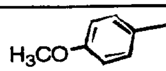
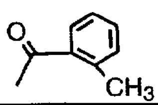
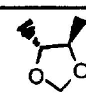
327			H	H	-CH_3	HRMS calc'd: 591.2971 found: 591.2966 m.p.=195-200°C
329			H	H	-CH_3	m.p. - 185-190°C (dec)
330			H	H	-CH_3	m.p. - 240-248°C (dec)
331			H	H	-CH_3	m.p. - 235-240°C (dec)
332			H	H	-CH_3	m.p. - 185-195°C (dec)
333			H	H	-CH_3	m.p. - 175-195°C (dec)
334			H	H	-CH_3	m.p. - 230-235°C (dec)
335			H	H	-CH_3	m.p. - 245-255°C (dec)
336			H	H	-CH_3	m.p. - 250-255°C (dec)

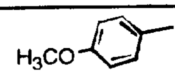
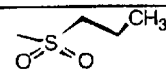
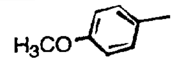
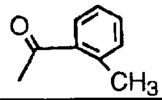
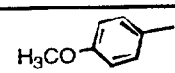
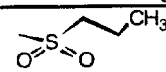
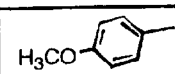
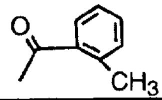
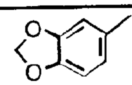
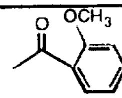
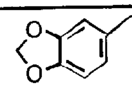
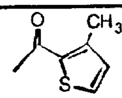
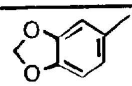
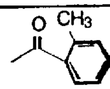
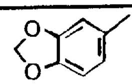
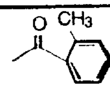
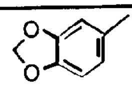
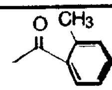
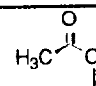
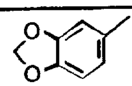
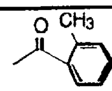
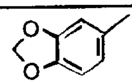
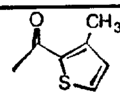
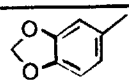
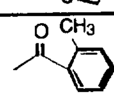
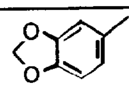
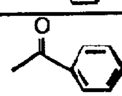
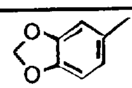
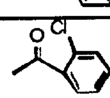
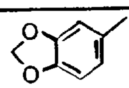
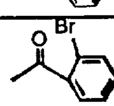
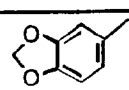
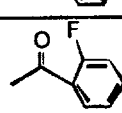
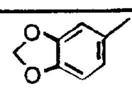
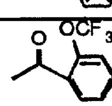


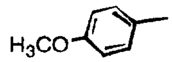
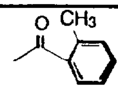
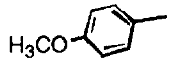
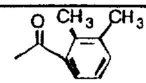
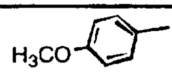
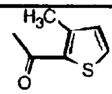
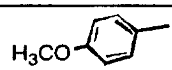
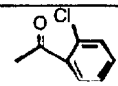
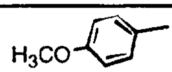
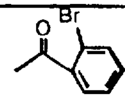
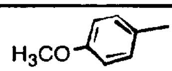
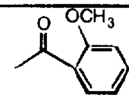
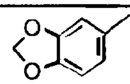
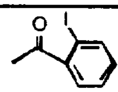
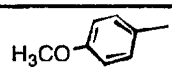
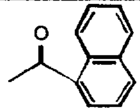
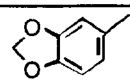
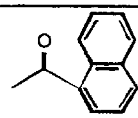
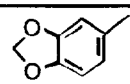
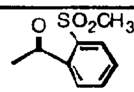
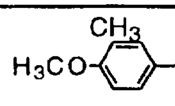
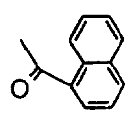
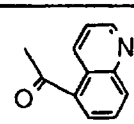
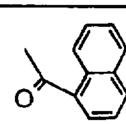
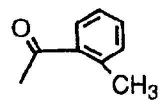
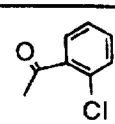
No.	R	W	R¹, R²¹	X	Physical Data
337				-CH_2-	LRMS: calc'd: 582 found: 583
338			=O	-CH_2-	LRMS: calc'd: 538 found: 539
339				-CH_2-	LRMS: calc'd: 574 found: 575

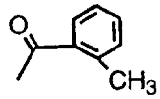
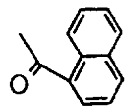
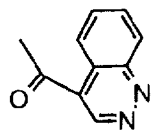
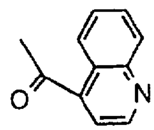
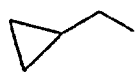
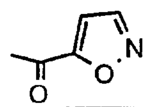
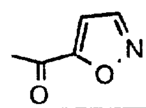
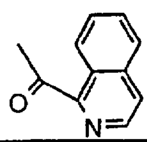
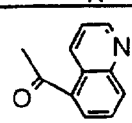
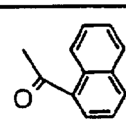
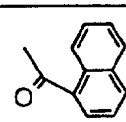
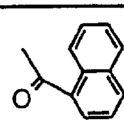
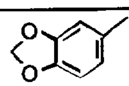
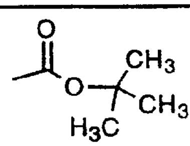
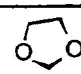
340				$-CH_2-$	LRMS: calc'd: 584 found: 585
341			=O	$-CH_2-$	LRMS: calc'd: 540 found: 541
342			H, OH	$-CH_2-$	LRMS: calc'd: 526 found: 527
436				$-SO_2-$	LRMS: calc'd: 632 found: 633
437				$-SO_2-$	LRMS: calc'd: 646 found: 647
438				$-SO_2-$	LRMS: calc'd: 558 found (M+H): 559
439				$-SO_2-$	LRMS: calc'd: 572 found (M+H): 573
440				$-SO_2-$	LRMS (FAB): calc'd (M+H): 591 found: 591
441				$-SO_2-$	LRMS (FAB): calc'd: 600 found (M+H): 601
442				$-SO_2-$	LRMS (FAB): calc'd: 626 found (M+H): 627
443				$-CH_2-$	LRMS: calc'd: 592 found (M+H): 593
444				$-SO_2-$	LRMS: calc'd: 626 found (M+H): 627
445				$-SO_2-$	LRMS: calc'd: 634 found (M+H): 635
446				$-SO_2-$	LRMS: calc'd: 620 found (M+H): 621
447				$-SO_2-$	LRMS: calc'd: 646 found (M+H): 647
448				$-SO_2-$	LRMS: calc'd: 606 found (M+H): 607
449				$-SO_2-$	LRMS: calc'd: 660 found (M+H): 661

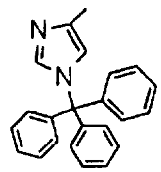
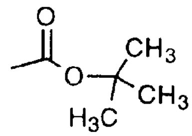
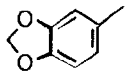
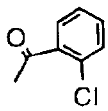
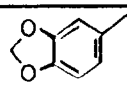
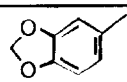
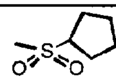
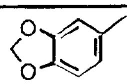
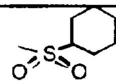
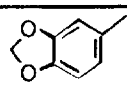
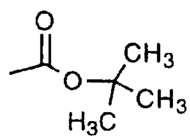
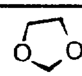
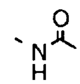
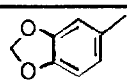
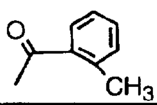
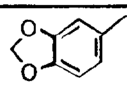
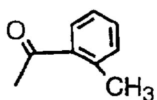
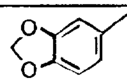
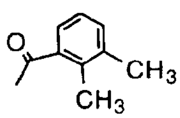
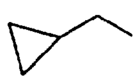
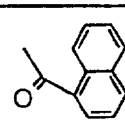
450				-SO_2-	LRMS: calc'd: 652 found (M+H): 653
451				-SO-	LRMS: calc'd: 592 found (M+H): 593
452				-SO-	LRMS: calc'd: 622 found (M+H): 623
453				-SO-	LRMS: calc'd: 618 found (M+H): 619
454				-SO-	LRMS: calc'd: 602 found (M+H): 603
455				-SO-	LRMS: calc'd: 630 found (M+H): 631
456				-SO_2-	LRMS: calc'd: 650 found (M+H): 651
457				-SO_2-	LRMS: calc'd: 638 found (M+H): 639
458				-SO-	LRMS: calc'd: 634 found (M+H): 635
459				-S-	LRMS: calc'd: 586 found (M+H): 587
460				-S-	LRMS: calc'd: 574 found (M+H): 575
461				-S-	LRMS: calc'd: 614 found (M+H): 615
462				-S-	LRMS: calc'd: 618 found (M+H): 619
463				-S-	LRMS: calc'd: 606 found (M+H): 607
464				-S-	LRMS: calc'd: 602 found (M+H): 603
465				-SO_2-	LRMS: calc'd: 596 found (M+H): 597
466		H		-SO_2-	LRMS: calc'd: 500 found (M+H): 501

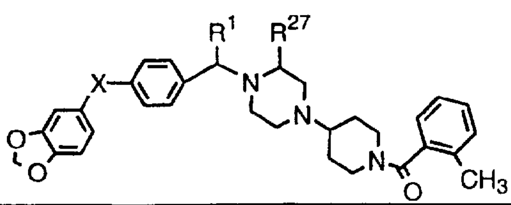
467				$-SO_2-$	LRMS: calc'd: 691 found (M+H): 692
468				$-SO_2-$	LRMS: calc'd: 705 found (M+H): 706
469				$-SO_2-$	LRMS: calc'd: 662 found (M+H):663
470				$-SO_2-$	LRMS: calc'd: 620 found (M+H):621
471				$-SO_2-$	LRMS: calc'd: 654 found (M+H): 655
472				-S-	LRMS: calc'd: 584 found (M+H): 585
473				-SO-	LRMS: calc'd: 600 found (M+H): 601
474				$-SO_2-$	LRMS: calc'd: 616 found (M+H): 617
475			OH, $(CH_2)_3OH$	-SO-	LRMS: calc'd: 618 found (M+H): 619
476			OH, $(CH_2)_3OH$	$-SO_2-$	LRMS: calc'd: 634 found (M+H): 635
477				$-SO_2-$	LRMS: calc'd: 592 found (M+H): 593
478				$-SO_2-$	LRMS: calc'd: 620 found (M+H): 621
479				$-SO_2-$	LRMS: calc'd: 604 found (M+H): 605
480				$-SO_2-$	LRMS: calc'd: 632 found (M+H): 633

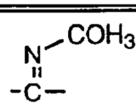
481				$-SO_2-$	LRMS: calc'd: 625 found (M+H): 625
482				$-SO_2-$	LRMS: calc'd: 636 found (M+H): 637
483				-SO-	LRMS: calc'd: 576 found (M+H): 577
484				-SO-	LRMS: calc'd: 588 found (M+H): 589
488			=O	$-SO_2-$	LRMS: calc's: 590 found: 591
489			=O	$-SO_2-$	LRMS: calc's: 580 found: 581
490			H, OH	$-SO_2-$	LRMS: calc's: 576 found: 577
491			CH_3, OH	$-SO_2-$	LRMS: calc's: 590 found: 591
492				$-SO_2-$	LRMS: calc's: 618 found: 619
493			=O	-S-	LRMS: calc's: 542 found (M+H): 543
502			H, H	$-SO_2-$	LRMS: calc's: 566 found: 567
503			H, H	$-SO_2-$	LRMS: calc's: 576 found: 577
504			H, H	$-SO_2-$	LRMS: calc's: 546 found: 547
505			H, H	$-SO_2-$	LRMS: calc's: 581 found: 581
506			H, H	$-SO_2-$	LRMS: calc's: 625 found: 626
507			H, H	$-SO_2-$	LRMS: calc's: 564 found: 565
508			H, H	$-SO_2-$	LRMS: calc's: 630 found: 631

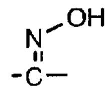
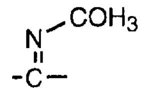
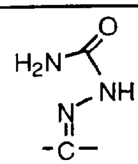
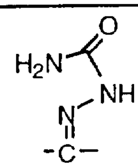
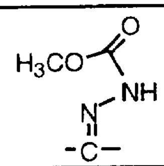
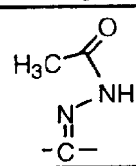
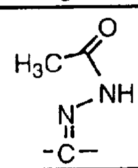
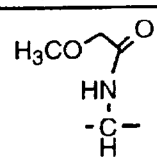
509			H, H	-SO_2-	LRMS: calc's: 546 found: 547
510			H, H	-SO_2-	LRMS: calc's: 560 found: 561
511			H, H	-SO_2-	LRMS: calc's: 552 found: 553
512			H, H	-SO_2-	LRMS: calc's: 567 found: 567
513			H, H	-SO_2-	LRMS: calc's:611.6 found: 613
514			H, H	-SO_2-	LRMS: calc's:562 found: 563
515			H, H	-SO_2-	LRMS: calc's:672 found:673
516			H, H	-SO_2-	LRMS: calc's:582 found:583
517			H, H	-SO_2-	LRMS: calc's:596 found:597
518			H, H	-SO_2-	LRMS: calc's:624 found:625
519			H, H	-SO_2-	LRMS: calc's:596 found ($M+H^+$):597
563	$(CH_3)_2CH_2$-		H, H	-S-	HRMS: calc'd (M+1): 488.2736 found: 488.2728
564	$(CH_3)_2CH_2$-		H, H	-SO_2-	HRMS: calc'd (M+1): 519.2681 found: 519.2685
565	$(CH_3)_2CH_2$-		H, H	-SO_2-	HRMS: calc'd (M+1): 483.2681 found: 483.2688
566	$(CH_3)_2CH_2$-		H, H	-SO_2-	HRMS: calc'd (M+1): 503.2135 found: 503.2144

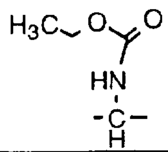
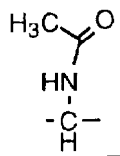
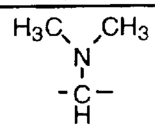
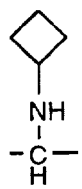
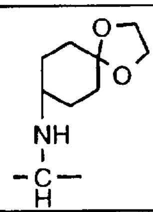
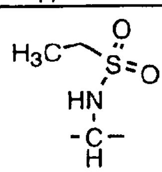
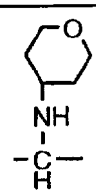
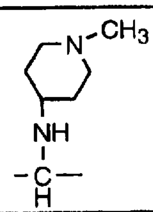
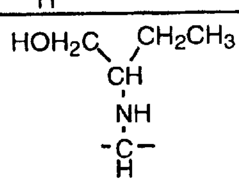
567	$(CH_3)_2CH_2$-		H, H	-S-	HRMS: calc'd (M+1): 451.2873 found: 451.2870
568	$(CH_3)_2CH_2$-		H, H	-CH_2-	HRMS: calc'd (M+1): 469.3219 found: 469.3219
569	$(CH_3)_2CH_2$-		H, H	-S-	HRMS: calc'd (M+1): 489.2688 found: 489.2687
570	$(CH_3)_2CH_2$-		H, H	-S-	HRMS: calc'd (M+1): 488.2736 found: 488.2739
571			H, H	-O-	HRMS: calc'd (M+1): 424.2600 found: 424.2608
572	-CH_3		H, H	-O-	HRMS: calc'd (M+1): 384.2287 found: 384.2294
573	$(CH_3)_2CH_2$-		H, H	-S-	HRMS: calc'd (M+1): 488.2736 found: 488.2751
574	$(CH_3)_2CH_2$-		H, H	-O-	HRMS: calc'd (M+1): 472.2964 found: 472.2964
575	$(CH_3)_2CH_2$-		H, H	-SO-	HRMS: calc'd (M+1): 503.2732 found: 503.2723
576	$CH_3CH_2SO_2$-		H, H	-NH-	LRMS: calc'd: 519 found ($M+H^+$): 520
577	-CH_3		H, H	-NH-	LRMS: calc'd: 441 found ($M+H^+$): 442
578				=O	LRMS: calc'd: 564 found: 565

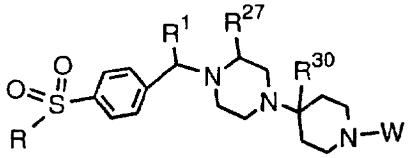
579				OH —C—	LRMS: calc'd: 754 found: 755
580				=O	LRMS: calc'd: 603 found: 603
581		$-SO_2(CH_2)_2CH_3$		=O	LRMS: calc'd: 570 found: 571
582				=O	LRMS: calc'd: 596 found: 597
583				=O	LRMS: calc'd: 610 found: 611
584					LRMS: calc'd: 579 found: 580
585			H, OH	=O	LRMS: calc'd: 528 found: 529
586			H, H	=O	LRMS: calc'd: 512 found: 513
590			H, H	$-SO_2-$	LRMS: calc'd: 574 found: 575
591			H, H	-O-	HRMS: calc'd (M+1): 483.3012 found: 483.3008

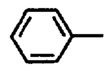
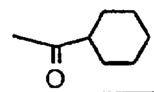
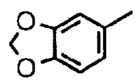
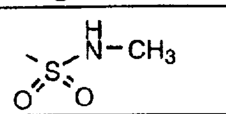
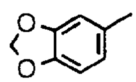
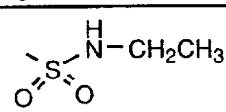
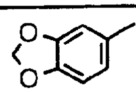
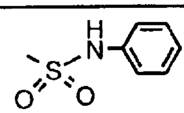
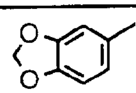
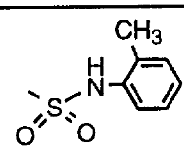
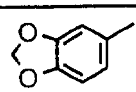
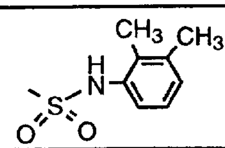
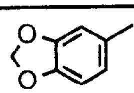
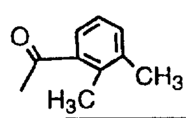
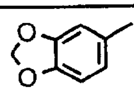
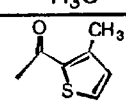
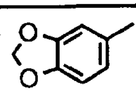
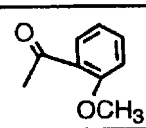
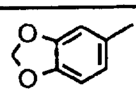
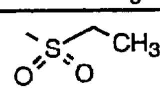
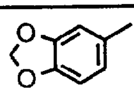
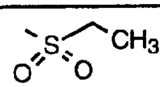
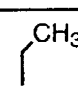
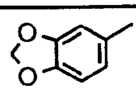
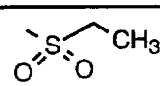


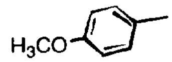
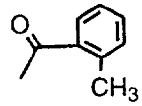
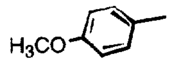
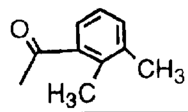
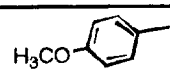
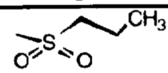
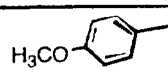
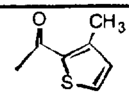
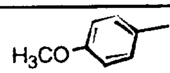
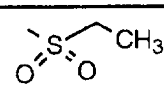
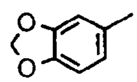
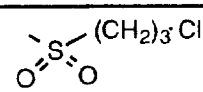
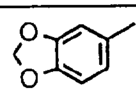
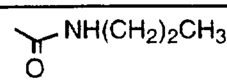
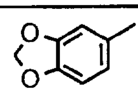
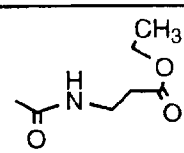
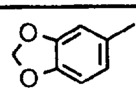
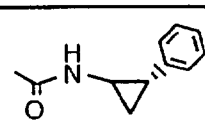
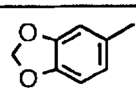
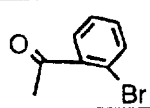
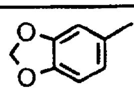
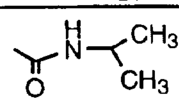
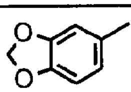
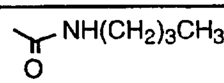
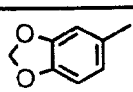
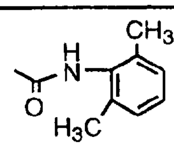
No.	X	R^1	R^{27}	Physical Data
533		H	H	MS (fFAB): 555.4 (M+1), 391,307

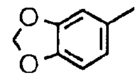
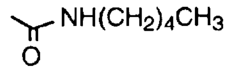
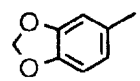
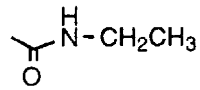
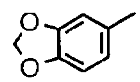
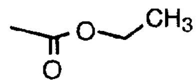
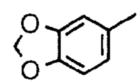
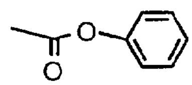
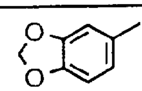
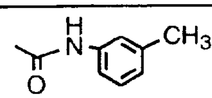
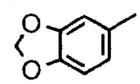
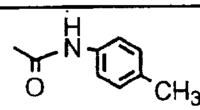
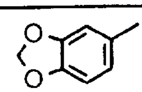
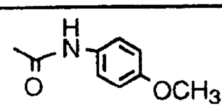
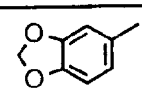
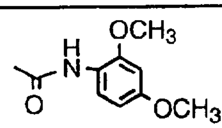
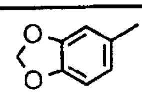
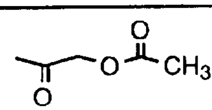
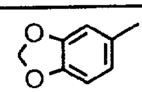
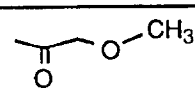
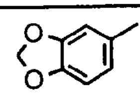
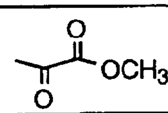
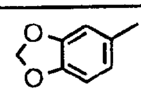
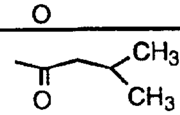
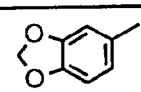
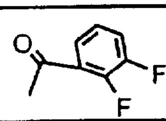
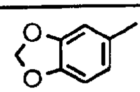
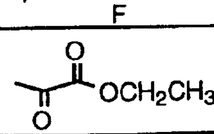
534		CH_3	CH_3	MS (fFAB): 569.4 (M+1), 553,302
535		CH_3	CH_3	MS (fFAB): 583.4 (M+1), 302, 282
536		CH_3	CH_3	MS (fFAB): 611 (M+1), 554 (isomer A)
537		CH_3	CH_3	MS (fFAB): 611 (M+1), 325 (isomer B)
538		CH_3	CH_3	MS (fFAB): 626.4 (M+1), 554
539		CH_3	CH_3	MS (fFAB): 610.3 (M+1), 460 (isomer A)
540		CH_3	CH_3	MS (fFAB): 610.2 (M+1), 554, 309 (isomer B)
541		CH_3	CH_3	MS (electrospray): 620 (M+1), 551,433 (isomer A)
542		CH_3	CH_3	MS (electrospray): 620 (M+1), 551,433 (isomer B)
543		H	H	MS (fFAB): 599.4 (M+1), 510, 277

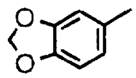
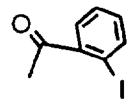
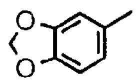
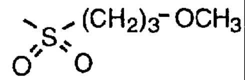
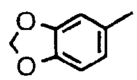
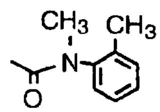
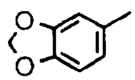
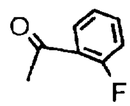
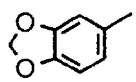
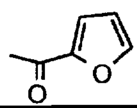
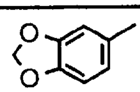
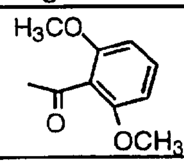
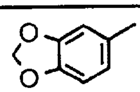
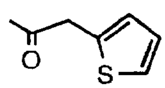
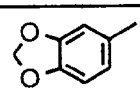
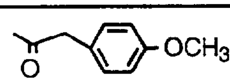
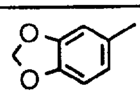
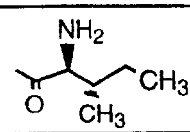
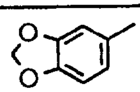
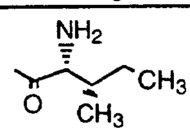
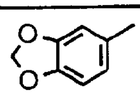
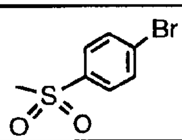
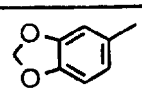
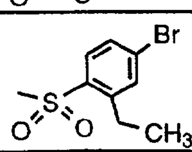
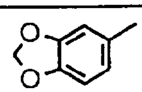
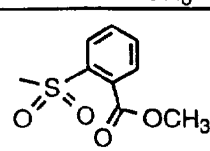
544		CH_3	CH_3	MS (fFAB): 627.4 (M+1), 326, 302
545		CH_3	CH_3	MS (fFAB): 597.5 (M+1), 302
546		H	H	MS (electrospray): 555 (M+1), 510,392
547		H	H	MS (fFAB): 581.4 (M+1), 510
548		H	H	MS (fFAB): 667.4 (M+1), 510
549		H	H	MS (electrospray): 619.2 (M+1), 510
550		H	H	FAB(MH+) = 611
551		H	H	MS (electrospray): 624.2 (M+1), 510
552		H	H	MS (electrospray): 599.2 (M+1), 510

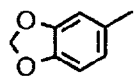
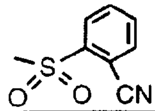
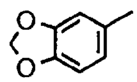
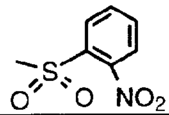
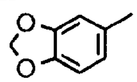
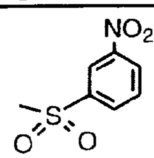
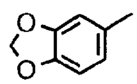
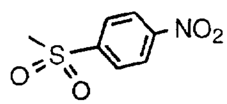
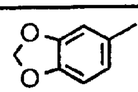
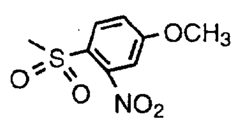
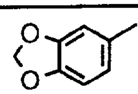
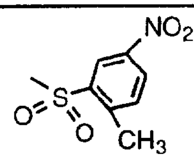
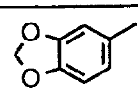
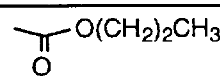
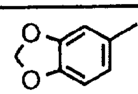
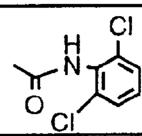
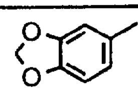
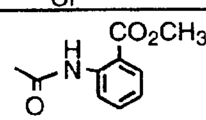
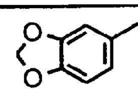
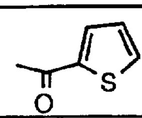
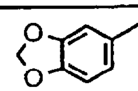
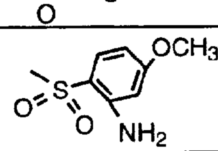
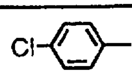
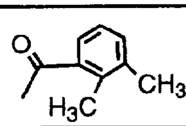


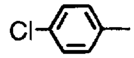
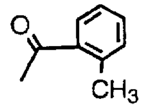
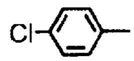
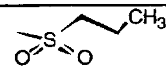
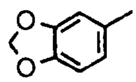
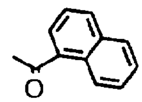
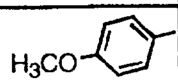
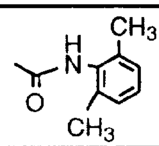
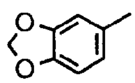
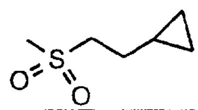
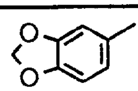
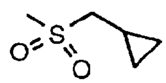
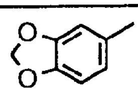
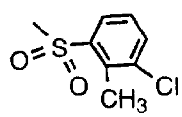
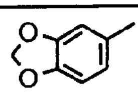
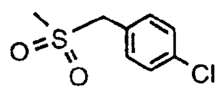
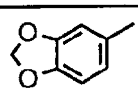
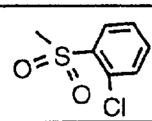
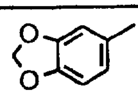
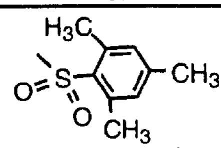
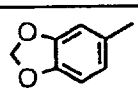
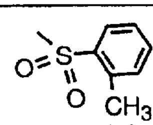
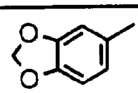
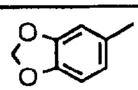
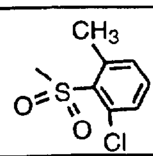
No.	R	W	R^1	R^{27}	R^{30}	Physical Data
343			H	H	$-CH_3$	MS (electrospray): 524.1 (M+1), 373
344			CH_3	CH_3	$-CH_3$	MH+ = 579
345			CH_3	CH_3	$-CH_3$	MH+ = 593
346			CH_3	CH_3	$-CH_3$	MH+ = 641
347			CH_3	CH_3	$-CH_3$	MH+ = 655
348			CH_3	CH_3	$-CH_3$	MH+ = 669
349			CH_3	CH_3	$-CH_3$	FAB (MH+) = 618
350			CH_3	CH_3	$-CH_3$	FAB (MH+) = 610
351			CH_3	CH_3	$-CH_3$	FAB (MH+) = 620
352			CH_3	CH_3	$-CH_3$	FAB (MH+) = 578
353			CH_3	CH_3		FAB (MH+) = 592
354			CH_3	CH_3		FAB (MH+) = 590

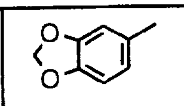
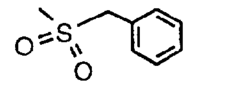
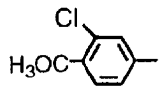
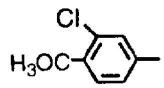
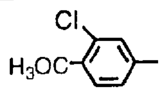
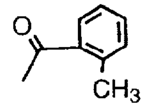
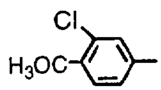
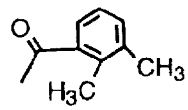
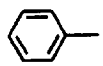
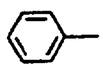
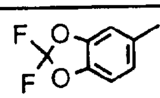
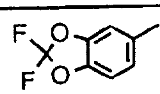
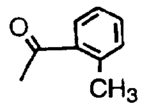
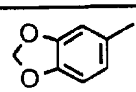
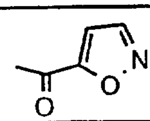
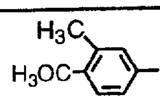
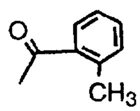
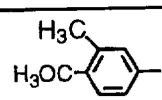
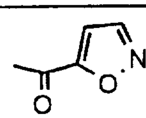
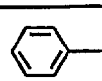
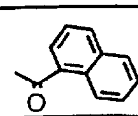
355			CH_3	CH_3	$-CH_3$	m.p. = 233-235°C (dec)
356			CH_3	CH_3	$-CH_3$	m.p. = 237-239°C (dec)
357			CH_3	CH_3	$-CH_3$	m.p. = 228-229°C (dec)
358			CH_3	CH_3	$-CH_3$	m.p. = 231-233°C (dec)
359			CH_3	CH_3	$-CH_3$	FAB(MH+) = 564
360			CH_3	CH_3	$-CH_3$	m.p. = 225-226°C (dec)
361			CH_3	CH_3	$-CH_3$	FAB(MH+) = 571
362			CH_3	CH_3	$-CH_3$	FAB(MH+) = 629
363			CH_3	CH_3	$-CH_3$	FAB(MH+) = 645
364			CH_3	CH_3	$-CH_3$	FAB(MH+) = 670,668
365			CH_3	CH_3	$-CH_3$	FAB(MH+) = 571
366			CH_3	CH_3	$-CH_3$	FAB(MH+) = 585
367			CH_3	CH_3	$-CH_3$	FAB(MH+) = 632

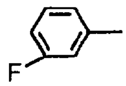
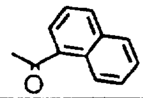
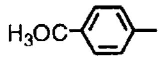
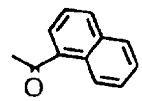
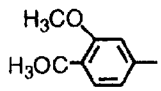
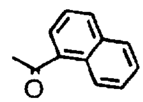
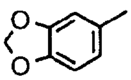
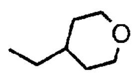
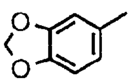
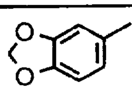
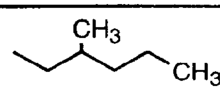
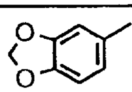
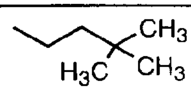
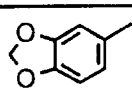
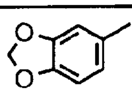
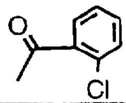
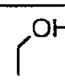
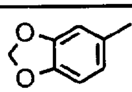
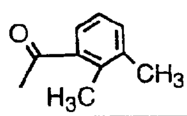
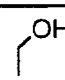
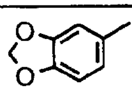
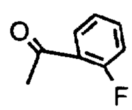
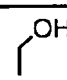
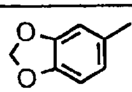
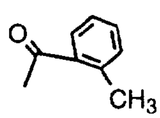
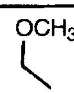
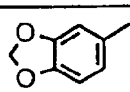
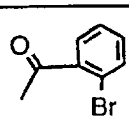
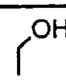
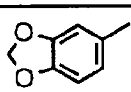
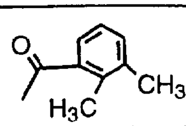
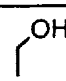
368			CH_3	CH_3	$-CH_3$	FAB(MH+) = 613
369			CH_3	CH_3	$-CH_3$	m.p. = 207-208°C (dec)
370			CH_3	CH_3	$-CH_3$	m.p. = 229-220°C (dec)
371			CH_3	CH_3	$-CH_3$	m.p. = 223-224°C (dec)
372			CH_3	CH_3	$-CH_3$	FAB(MH+) = 619
373			CH_3	CH_3	$-CH_3$	FAB(MH+) = 619
374			CH_3	CH_3	$-CH_3$	FAB(MH+) = 635
375			CH_3	CH_3	$-CH_3$	FAB(MH+) = 665
376			CH_3	CH_3	$-CH_3$	FAB(MH+) = 586
377			CH_3	CH_3	$-CH_3$	FAB(MH+) = 558
378			CH_3	CH_3	$-CH_3$	FAB(MH+) = 572
379			CH_3	CH_3	$-CH_3$	FAB(MH+) = 570
380			CH_3	CH_3	$-CH_3$	FAB(MH+) = 626
381			CH_3	CH_3	$-CH_3$	FAB(MH+) = 586

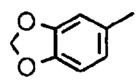
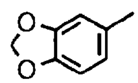
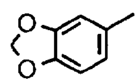
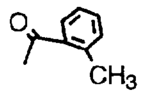
382			CH_3	CH_3	$-CH_3$	FAB(MH+) = 716
383			CH_3	CH_3	$-CH_3$	m.p. = 230-231°C (dec)
384			CH_3	CH_3	$-CH_3$	m.p. = 244-245°C (dec)
385			CH_3	CH_3	$-CH_3$	FAB(MH+) = 608
386			CH_3	CH_3	$-CH_3$	FAB(MH+) = 580
387			CH_3	CH_3	$-CH_3$	FAB(MH+) = 650
388			CH_3	CH_3	$-CH_3$	FAB(MH+) = 610
389			CH_3	CH_3	$-CH_3$	FAB(MH+) = 633
390			CH_3	CH_3	$-CH_3$	FAB(MH+) = 599
391			CH_3	CH_3	$-CH_3$	FAB(MH+) = 599
392			CH_3	CH_3	$-CH_3$	m.p. = 230-231°C (dec)
393			CH_3	CH_3	$-CH_3$	m.p. = 225-226°C (dec)
394			CH_3	CH_3	$-CH_3$	m.p. = 208-209°C (dec)

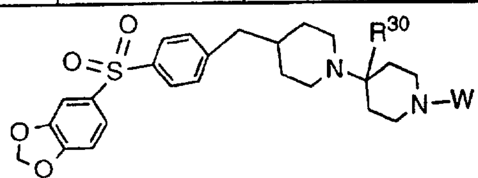
395			CH_3	CH_3	-CH_3	m.p. = 218-219°C (dec)
396			CH_3	CH_3	-CH_3	m.p. = 218-219°C (dec)
397			CH_3	CH_3	-CH_3	m.p. = 229-230°C (dec)
398			CH_3	CH_3	-CH_3	m.p. = 229-230°C (dec)
399			CH_3	CH_3	-CH_3	m.p. = 215-216°C (dec)
400			CH_3	CH_3	-CH_3	m.p. = 220-221°C (dec)
401			CH_3	CH_3	-CH_3	m.p. = 224-225°C (dec)
402			CH_3	CH_3	-CH_3	FAB(MH+) = 673
403			CH_3	CH_3	-CH_3	FAB(MH+) = 663
404			CH_3	CH_3	-CH_3	FAB(MH+) = 596
405			CH_3	CH_3	-CH_3	FAB(MH+) = 671
406			CH_3	CH_3	-CH_3	FAB(MH+) = 608

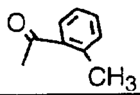
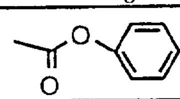
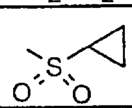
407			CH_3	CH_3	$-CH_3$	FAB(MH+) = 594
408			CH_3	CH_3	$-CH_3$	FAB(MH+) = 582
409			CH_3	CH_3	$-CH_3$	FAB(MH+) = 640
410			CH_3	CH_3	$-CH_3$	FAB(MH+) = 619
411			CH_3	CH_3	$-CH_3$	LRMS: calc'd:617 found ($M+H^+$): 618
412			CH_3	CH_3	$-CH_3$	LRMS: calc'd:603 found ($M+H^+$): 604
413			CH_3	CH_3	$-CH_3$	LRMS: calc'd:673 found ($M+H^+$): 674
414			CH_3	CH_3	$-CH_3$	LRMS: calc'd:673 found ($M+H^+$): 674
415			CH_3	CH_3	$-CH_3$	LRMS: calc'd:659 found ($M+H^+$): 660
416			CH_3	CH_3	$-CH_3$	LRMS: calc'd:667 found ($M+H^+$): 668
417			CH_3	CH_3	$-CH_3$	LRMS: calc'd:639 found ($M+H^+$): 640
418		$-SO_2(CH_2)_2CF_3$	CH_3	CH_3	$-CH_3$	LRMS: calc'd:645 found ($M+H^+$): 646
419			CH_3	CH_3	$-CH_3$	LRMS: calc'd:673 found ($M+H^+$): 674

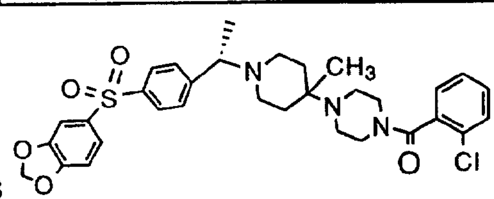
420			CH_3	CH_3	$-CH_3$	LRMS: calc'd:639 found ($M+H^+$): 640
421		$-SO_2(CH_2)_2CH_3$	CH_3	CH_3	$-CH_3$	LRMS: calc'd:611 found ($M+H^+$): 612
422		$-SO_2CH_2CH_3$	CH_3	CH_3	$-CH_3$	LRMS: calc'd:597 found ($M+H^+$): 598
423			CH_3	CH_3	$-CH_3$	LRMS: calc'd:623 found ($M+H^+$): 624
424			CH_3	CH_3	$-CH_3$	LRMS: calc'd:637 found ($M+H^+$): 637
425		$-SO_2(CH_2)_2CH_3$	CH_3	CH_3	$-CH_3$	LRMS: calc'd:547 found ($M+H^+$): 548
426		$-SO_2CH_2CH_3$	CH_3	CH_3	$-CH_3$	LRMS: calc'd:533 found ($M+H^+$): 534
427		$-SO_2(CH_2)_2CH_3$	CH_3	CH_3	$-CH_3$	LRMS: calc'd:627 found ($M+H^+$): 628
428			CH_3	CH_3	$-CH_3$	LRMS: calc'd:639 found ($M+H^+$): 640
429			CH_3	CH_3	$-CH_3$	LRMS: calc'd:580 found ($M+H^+$): 581
430			CH_3	CH_3	$-CH_3$	LRMS: calc'd:603 found ($M+H^+$): 604
431			CH_3	CH_3	$-CH_3$	LRMS: calc'd:580 found ($M+H^+$): 581
432			CH_3	CH_3	$-CH_3$	LRMS: calc'd:595 found ($M+H^+$): 596

433			CH_3	CH_3	$-CH_3$	LRMS: calc'd:613 found $(M+H^+)$: 614
434			CH_3	CH_3	$-CH_3$	LRMS: calc'd:626 found $(M+H^+)$: 627
435			CH_3	CH_3	$-CH_3$	LRMS: calc'd:655 found $(M+H^+)$: 656
528			CH_3	CH_3	$-CH_3$	m.p. = 212-214°C (dec)
529		$-CH_2CH_2CH_3$	CH_3	CH_3	$-CH_3$	m.p. = 215-217°C (dec)
530			CH_3	CH_3	$-CH_3$	m.p. = 210-211°C (dec)
531			CH_3	CH_3	$-CH_3$	m.p. = 223-225°C (dec)
532			CH_3	CH_3	$-CH_3$	m.p. = 209-211°C (dec)
563			H	H		HRMS calc'd: 612.1935 found: 612.1952 m.p.=187-197°C
564			H	H		HRMS calc'd: 606.2638 found: 606.2638 m.p.=185-195°C
565			H	H		m.p. = 178-188°C
566			H	H		HRMS calc'd: 606.2638 found: 606.2633 m.p.=175-183°C
567			H	H		HRMS calc'd: 656.1430 found: 656.1438 m.p.=185-192°C
568			CH_3	CH_3		HRMS calc'd: 634.2951 found: 634.2968 m.p.=185-195°C

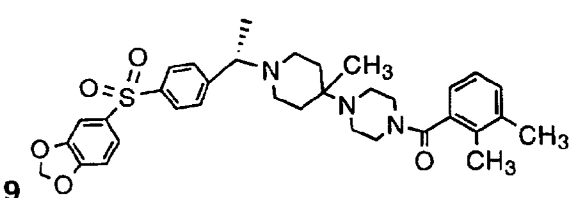
569		$-SO_2(CH_2)_2CH_3$	CH_3	CH_3	OH	HRMS calc'd: 608.2464 found: 608.2477 m.p.=205-215°C
570		$-SO_2CH_2CH_3$	CH_3	CH_3	OH	HRMS calc'd: 594.2308 found: 594.2311 m.p.=175-185°C
571			CH_3	CH_3	OH	HRMS calc'd: 620.2794 found: 620.2805 m.p.=185-190°C



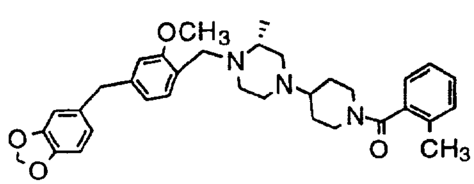
No.	W	R^{30}	Physical Data
553	$-SO_2(CH_2)_2CH_3$	-CN	LRMS: calc'd: 573;found $(M+1)^+$: 574
554		$-CH_3$	LRMS: calc'd: 574 found $(M+1)^+$: 575
555		$-CH_3$	LRMS: calc'd: 576 found $(M+1)^+$: 577
556	$-SO_2CH_2CH_3$	$-CH_3$	LRMS: calc'd: 548; found $(M+1)^+$: 549
557	$-SO_2CH_2CF_3$	$-CH_3$	LRMS: calc'd: 602; found $(M+1)^+$: 603
558		$-CH_3$	LRMS: calc'd: 560 found $(M+1)^+$: 561



588 MH+ = 610



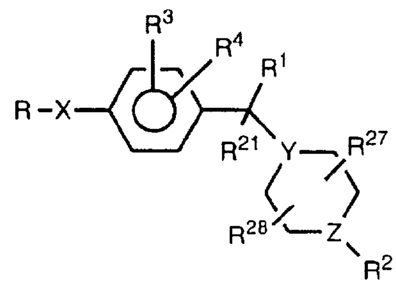
589 MH+ = 604



594 MH+ = 596

What is Claimed:

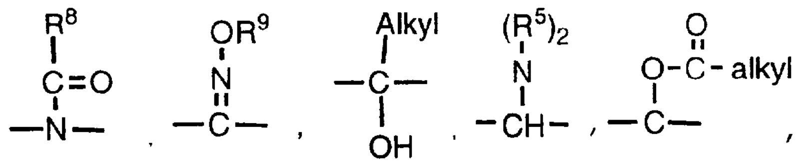
1. A compound having the structural formula

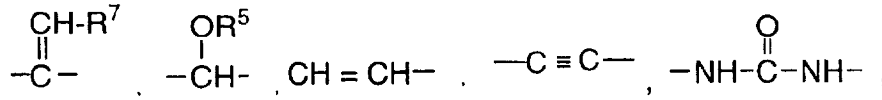


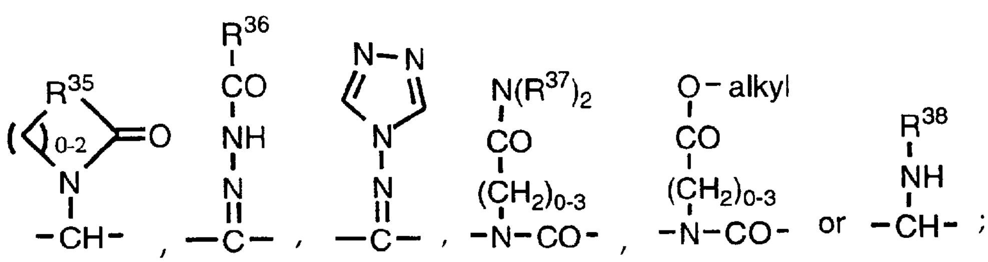
including all isomers and pharmaceutically acceptable salts, esters, and solvates thereof,

wherein one of Y and Z is N and the other is N, CH, or C-alkyl;

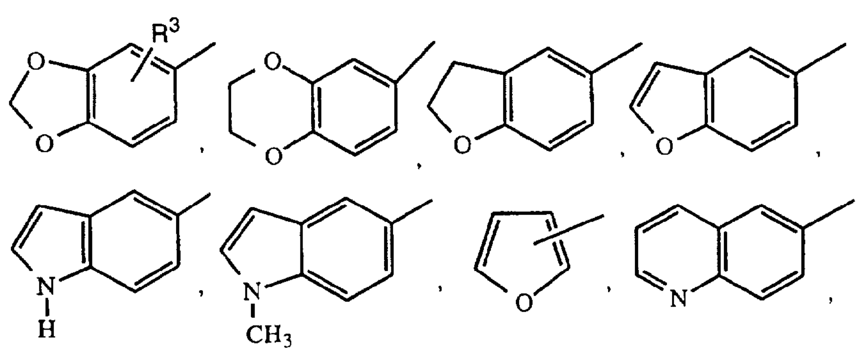
X is -O-, -S-, -SO-, $-SO_2-$, $-NR^6-$, -CO-, $-CH_2-$, -CS-, $-C(OR^5)_2-$, $-C(SR^5)_2-$, $-CONR^{20}-$, $-C(alkyl)_2-$, -C(H)(alkyl)-, $-NR^{20}-SO_2-$, $-SO_2-NR^{20}-$, $-NR^{20}CO-$, -O-CO-NH-, -NH-CO-O-,

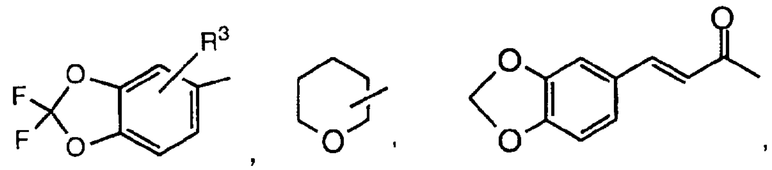


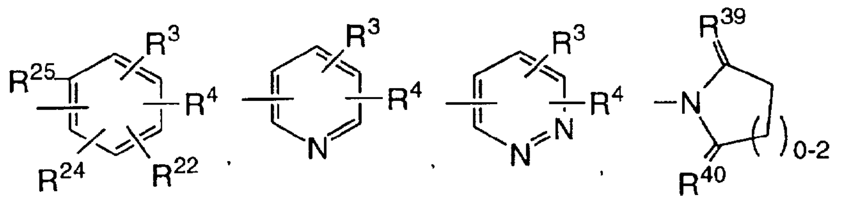


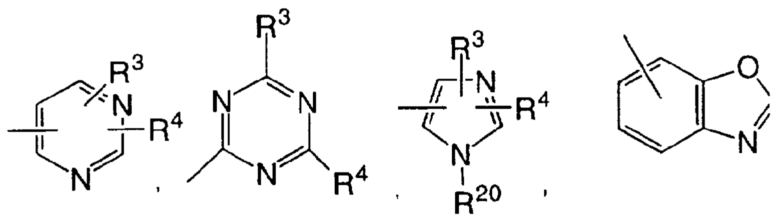


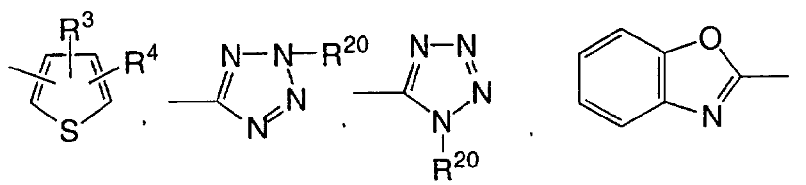
R is



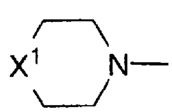




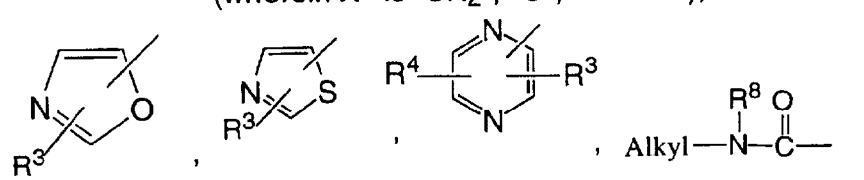


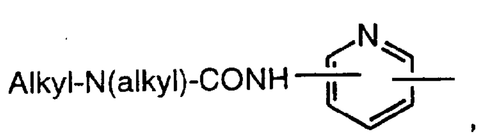


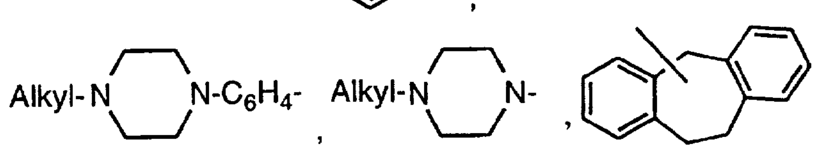
$R^7-C\equiv C-CH(R^8)-$, $R^7-CH_2-C\equiv C-$, $(R^8)_2C=C=C(R^7)-$,

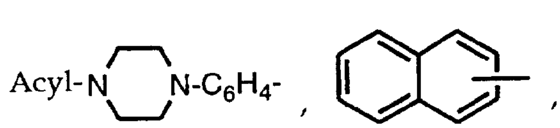


(wherein X^1 is $-CH_2-$, $-O-$, or $-NR^7-$),



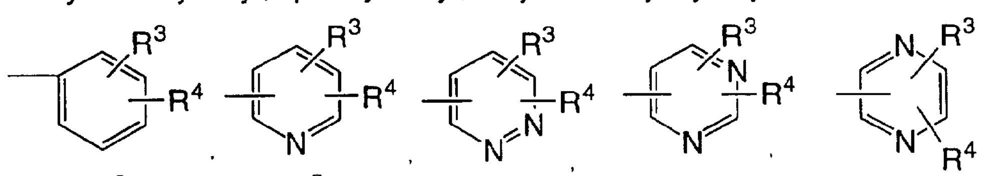


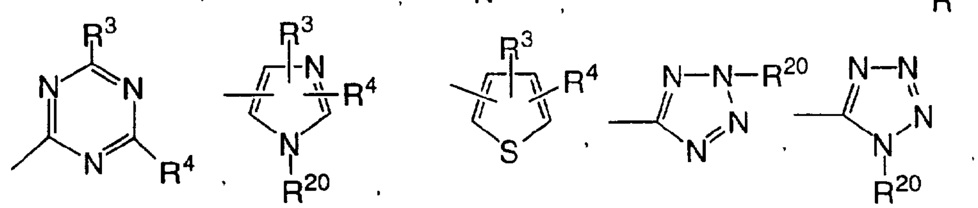


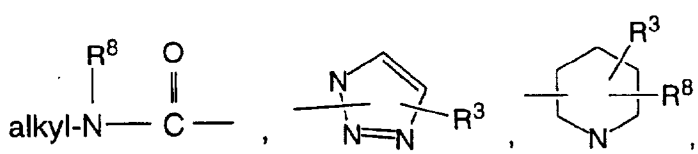


hydrogen, acyl, alkyl, alkoxy, alkenyl, cycloalkyl, cycloalkyl substituted with one or two groups selected from the group consisting of alkyl and carbonyl, cycloalkenyl, bicycloalkyl, arylalkenyl, benzyl, benzyl substituted with up to three independently selected R^3 groups, cycloalkylalkyl, polyhaloacyl, benzyloxyalkyl, hydroxyC_2-C_{20}alkyl, alkenylcarbonyl, alkylarylsulfonyl, alkoxycarbonylaminoacyl, alkylsulfonyl, or arylsulfonyl, additionally, when X is -CH_2-, R may also be -OH; in further addition, when X is not N, R may also be hydroxymethyl, in further addition, R and X may combine to form the group Prot-$(NOAA)_r$-NH- wherein r is an integer of 1 to 4, Prot is a nitrogen protecting group and when r is 1, NOAA is a naturally occuring amino acid or an enantiomer thereof, or when r is 2 to 4, each NOAA is a peptide of an independently selected naturally occuring amino acid or an enantiomer thereof;

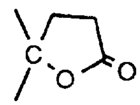
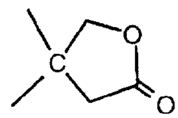
R^1 and R^{21} are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkyl, alkynyl, cyano, aminoalkyl, alkoxycarbonyl, aminocarbonyl, hydroxyamidino, alkoxycarbonylalkyl, phenyl alkyl, alkylcarbonlyoxyalkyl,





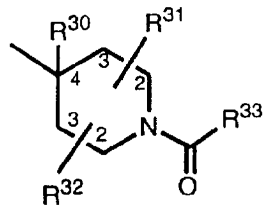
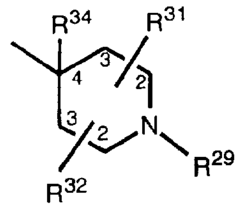


H, —OH, (provided R^1 and R^{21} are both not —OH and Y is not N), formyl, —CO alkyl, -COacyl, —COaryl, and hydroxyalkyl; additionally R^1 and R^{21} together may form the group $=CH_2$, $=N\text{-}OR^5$, =N-CN, $=N\text{-}N(R^5)_2$, =CH-alkyl, alkylene, $=\overset{\text{alkyl}}{\overset{|}{C}}-\text{alkyl}$ or $=C(\text{halo})_2$; in further addition, R^1

and R^{21} together with the carbon atom to which they are attached may form the group  or 

or R^1 and R^{21} together with the carbon atom to which they are attached may form a saturated heterocyclic ring containing 3 to 7 carbon atoms, one or more of which may be optionally substituted by alkyl, and one or two groups independently selected from S, O, and N-R^{20};

R^2 is

 or  ;

R^3, R^4, R^{22}, R^{24}, and R^{25} are independently selected from the group consisting of alkyl, H, halo, alkoxy, benzyloxy, benzyloxy substituted by nitro or aminoalkyl, haloalkyl, polyhaloalkyl, nitro, cyano, sulfonyl, hydroxy, amino, alkylamino, formyl, alkylthio, polyhaloalkoxy, acyloxy, trialkylsilyl, alkylsulfonyl, arylsulfonyl, acyl, alkoxycarbonyl alkylsulfinyl; $-OCONH_2$, -OCONH-alkyl, alkylaminoalkyl, dialkylaminoalkyl, -COOH, $-CON(R^{20})_2$, $-OCON(alkyl)_2$, -NHCOO-alkyl, -NHCO-alkyl, phenyl, hydroxyalkyl, or morpholino;

each R^5 and R^6 is independently selected from the group consisting of H and alkyl, provided that when X is $C(OR^5)_2$ or $C(SR^5)_2$, both R^5 groups cannot be H, and in addition, when X is $C(OR^5)_2$ or $C(SR^5)_2$, the two R^5 groups in X may be joined to form $—(CR^{20}{}_2)_p$- wherein p is an integer of 2 to 4;

R^7 is independently selected from the group consisting of H, alkyl, arylalkyl, cycloalkyl, aryl and aryl substituted with R^3 and R^4 as defined herein;

each R^8 is independently selected from the group consisting of H, hydroxyalkyl or alkyl, or two R^8 groups may be joined to form an alkylene group;

R^9 is H, alkyl, aralkyl, or acyl;

R^{20} is H, aryl or alkyl;

R^{27} and R^{28} are independently selected from the group consisting of H, alkyl, hydroxyalkyl, arylalkyl, aminoalkyl, haloalkyl, thioalkyl, alkylthioalkyl, carboxyalkyl, imidazolyalkyl, and indolyalkyl; or R^{27} and R^{28} may combine to form an alkylene group;

R^{29} is H, alkyl, -CO-alkyl, -CO-cycloalkyl, alkoxycarbonyl, aminocarbonyl, aryloxycarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylsulfonyl, arysulfonyl or $-SO_2-NH-R^{20}$;

R^{30} is H, alkyl, aryl, cycloalkyl, hydroxyalkyl, aminoalkyl, $-COOR^{20}$, $-CON(R^{20})_2$ or cyano;

R^{31} and R^{32} are the same as R^{30} and in addition, two R^{30}, R^{31} and R^{32} groups may form the group $-(CH_2)_r-$ (wherein r is 1 to 6), in further addition, R^{31} and R^{32} can also be hydroxy, $-N(R^{20})_2$, -O-acyl, $-N(R^{20})$acyl, $-OCOOR^{20}$, or $-OCON(R^{20})_2$;

R^{33} is aryl or heteroaryl, with the proviso that when R^{33} is heteroaryl, the $CO-R^{33}$ bond is to a carbon atom in the R^{33} group;

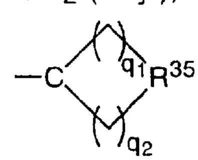
R^{34} is alkyl, cycloalkyl or aryl and in addition R^{34} may also be H when R^1 and R^{21} together with the carbon atom to which they are attached form a saturated heterocyclic ring containing 3 to 7 carbon atoms and two groups independently selected from S, O, and $N-R^{20}$;

R^{35} is $-CH_2-$, $-NR^{20}-$ or -O-;

R^{36} is $-NH_2$, alkyl or alkoxy;

R^{37} is independently selected from the group consisting of H and alkyl;

R^{38} is $-CO-(CH_2)_{0-5}-OR^5$, $-SO_2$-(alkyl), or



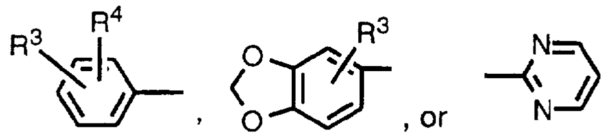
wherein q_1 and q_2 are independently 1-5, provided that the sum of q_1 and q_2 is 2-5; and

R^{39} and R^{40} are independently selected from the group consisting of =O and (H,H).

2. A compound of claim 1 wherein Y and Z are N

3. A compound of claim 1 wherein Y is CH and Z is N

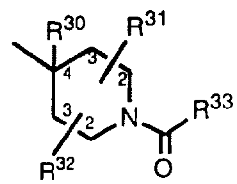
4. A compound of any of claims 1, 2 or 3 wherein R is



and X is O, SO, SO_2, CH_2, CH(alkyl), $C(alkyl)_2$, CH(OH), or $N(R^{20})CO$.

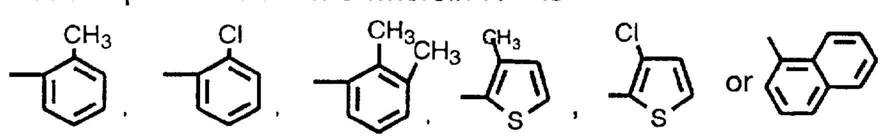
5. A compound of any of claims 1, 2, 3, 4 or 5 wherein R^3 and R^4 are H; either R^1 is H, cycloalkyl or alkyl and R^{21} is H or R^1 and R^{21} together form =O or  ; and wherein at least one of R^{27} and R^{28} is alkyl.

6. A compound of any of claims 1, 2, 3, 4 or 5 wherein R^2 is

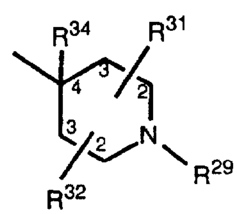


and R^{30} is H or CH_3: R^{31} and R^{32} are H: and R^{33} is ortho-substituted aryl or heteroaryl.

7. A compound of claim 6 wherein R^{33} is



8. A compound of any one of claims 1 to 5 wherein R^2 is



and R^{34} is methyl and R^{31} and R^{32} are H.

9. A compound as defined in claim 1 selected from the group consisting of compound numbers **17**, **18**,**25**, **30**, **31**, **32**, **34**, **35**, **36**,

37, 41, 43, 44, 49, 53, 54, 56, 57, 58, 59, 80, 82, 84, 85, 94, 98, 100, 108, 121, 126, 127, 137, 145, 151, 152, 154, 155, 162, 166, 178, 179, 181, 185, 190, 191, 194, 199, 214, 215, 216, 225, 247, 253, 256, 257, 337, 339, 340, 341, 349, 351, 367, 409, 459, 479, 488, 489, 490, 500, 501, 502, 503, 505, 506, 507, 515, 516, 517, 555 and 562 from the tables of compounds appearing in the specification.

10. A pharmaceutical composition which comprises a compound as defined in claim 1 in combination with a pharmaceutically acceptable carrier.

11. A process for the preparation of a pharmaceutical composition as defined in claim 10 comprising admixing a compound as claimed in any of claims 1 to 9 with a pharmaceutically acceptable carrier.

12. The use of a compound of claim 1 for the preparation of a medicament for treating a cognitive or neurodegenerative disease.

13. A kit for treating a cognitive or neurodegenerative disease comprising in separate containers in a single package pharmaceutical compounds for use in combination, in one container a compound in accordance with claim 1 and in a separate container an acetylcholinesterase inhibitor, said compound and inhibitor each being in a pharmaceutically acceptable carrier and their combined quantities being an effective amount.

14. A method for treating a cognitive or neurodegenerative disease comprising administering to a patient suffering from said disease an effective amount of a compound of claim 1, alone or in combination with an acetylcholinesterase inhibitor.

PCT

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C07D 409/14, 401/04, 413/14

A3

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(74) Agents: MAGATTI, Anita, W. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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With international search report.

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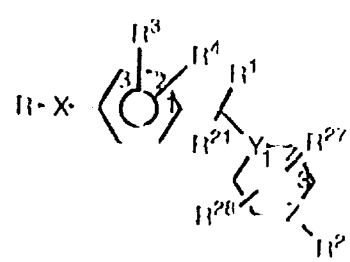
(54) Title: PIPERIDINE AND PIPERAZINE DERIVATIVES AND THEIR USE AS MUSCARINIC ANTAGONISTS



(I)

(57) Abstract

Di-N-substituted piperazine or 1,4 di-substituted piperidine compounds in accordance with formula I (including all isomers, salts, esters, and solvates) wherein R, R^1, R^2, R^3, R^4, R^{21}, R^{27}, R^{28}, X, Y and Z as defined herein are muscarinic antagonists useful for treating cognitive disorders such as Alzheimer's disease. Pharmaceutical compositions and methods of preparation are also disclosed. Also disclosed are synergistic combinations of compounds of the above formula with acetylcholinesterase inhibitors.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/13383

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D405/14 A61K31/495 C07D409/14 C07D401/04 C07D413/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 96 26196 A (SCHERING CORP) 29 August 1996 see the whole document ---	1-13
A	EP 0 711 763 A (SANTEN PHARMA CO LTD) 15 May 1996 see claim 1 ---	1
A	US 5 010 078 A (ABOU-GHARBIA MAGID A ET AL) 23 April 1991 see claim 1 ---	1
A	EP 0 343 961 A (AMERICAN HOME PROD) 29 November 1989 see claim 1 ---	1
A	US 2 792 398 A (KYRIDES) 14 May 1957 see claim 1 ---	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
28 October 1997	13.11.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, M

INTERNATIONAL SEARCH REPORT

Int ational Application No
PCT/US 97/13383

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 45, no. 12, 25 June 1951 Columbus, Ohio, US; abstract no. 5153, OCHIACHI ET AL: "Electrolytic reduction of the pyridinium ion." column 1; XP002044214 see abstract & IBID, pages 313-316, -----	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/13383

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 14
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/13383

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9626196 A	29-08-96	AU 4971796 A	11-09-96
EP 0711763 A	15-05-96	FI 960364 A	26-01-96
		NO 960270 A	23-01-96
		CA 2168264 A	09-02-95
		CN 1128026 A	31-07-96
		WO 9504050 A	09-02-95
		JP 7089949 A	04-04-95
US 5010078 A	23-04-91	US 5482940 A	09-01-96
		US 5380725 A	10-01-95
		US 5106849 A	21-04-92
		US 5278160 A	11-01-94
		US 5254552 A	19-10-93
		AT 132862 T	15-01-96
		AU 628341 B	17-09-92
		AU 3502589 A	30-11-89
		DE 68925385 D	22-02-96
		DE 68925385 T	15-05-96
		DK 249989 A	25-11-89
		EP 0343961 A	29-11-89
		ES 2081302 T	01-03-96
		FI 94130 B	13-04-95
		GB 2218988 A,B	29-11-89
		IE 64151 B	12-07-95
		IL 90279 A	30-03-95
		JP 2015059 A	18-01-90
		PT 90633 B	30-11-94
EP 0343961 A	29-11-89	AT 132862 T	15-01-96
		AU 628341 B	17-09-92
		AU 3502589 A	30-11-89
		DE 68925385 D	22-02-96
		DE 68925385 T	15-05-96
		DK 249989 A	25-11-89
		ES 2081302 T	01-03-96
		FI 94130 B	13-04-95
		GB 2218988 A,B	29-11-89
		IE 64151 B	12-07-95
		IL 90279 A	30-03-95

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 97/13383

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0343961 A		JP 2015059 A	18-01-90
		PT 90633 B	30-11-94
		US 5482940 A	09-01-96
		US 5380725 A	10-01-95
		US 5010078 A	23-04-91
		US 5106849 A	21-04-92
		US 5278160 A	11-01-94
		US 5254552 A	19-10-93
US 2792398 A	14-05-57	NONE	